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Expert panel consensus recommendations for ambulatory blood pressure monitoring in Asia: The HOPE Asia Network

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Abstract

Hypertension is an important public health issue because of its association with a number of significant diseases and adverse outcomes. However, there are important ethnic differences in the pathogenesis and cardio-/cerebrovascular consequences of hypertension. Given the large populations and rapidly aging demographic in Asian regions, optimal strategies to diagnose and manage hypertension are of high importance. Ambulatory

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blood pressure monitoring (ABPM) is an important out-of-office blood pressure (BP) measurement tool that should play a central role in hypertension detection and management. The use of ABPM is particularly important in Asia due to the specific features of hypertension in Asian patients, including a high prevalence of masked hypertension, disrupted BP variability with marked morning BP surge, and nocturnal hypertension. This HOPE Asia Network document summarizes region-specific literature on the relationship between ABPM parameters and cardiovascular risk and target organ damage, providing a rationale for consensus-based recommendations on the use of ABPM in Asia. The aim of these recommendations is to guide and improve clinical practice to facilitate optimal BP monitoring with the goal of optimizing patient management and expediting the efficient allocation of treatment and health care resources. This should contribute to the HOPE Asia Network mission of improving the management of hypertension and organ protection toward achieving "zero" cardiovascular events in Asia.

1 | INTRODUCTION

Hypertension is a significant public health issue, largely due to the contribution it makes to the risk of other serious diseases, including cardiovascular disease and stroke.[1,2] However, there are important ethnic differences in the pathogenesis and cardiovascular consequences of hypertension.[3-12] With large populations and the rapidly aging population demographic in Asian countries, the increasing burden of hypertension and associated comorbidities will have a growing and substantial negative economic and social impact in the region.[6,13-15] Therefore, optimizing strategies to detect and manage hypertension is of utmost importance.

Major international guidelines highlight the importance of out-of-office blood pressure (BP) monitoring in the diagnosis and management of hypertension.[13,16-23] The two main options available are home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM). Recommendations for the application of HBPM in Asian contexts are available,[24] but corresponding guidelines for the region-specific use of ABPM are lacking.

This document summarizes the evidence-based consensus recommendations of an expert panel on ABPM convened for Asia by the Hypertension, brain, cardiovascular and renal Outcome Prevention and Evidence in Asia (HOPE Asia) Network. It is anticipated that these recommendations will help guide clinical practice, contribute to the optimization of BP monitoring, and thus improve the management of hypertension in the region, with the ultimate goal of reducing the risk of cardiovascular events.

2 | MATERIALS AND METHODS

The expert panel's consensus recommendations were the output of a HOPE Asia Network meeting convened in Beijing, China, on September 21, 2018 during the 2018 Scientific Meeting of the International Society of Hypertension. The recommendations were based on a review of evidence from randomized controlled trials (RCTs), meta-analyses, and other relevant data on ABPM. Priority was given to data sourced from the Asia region to ensure that the recommendations would be applicable to a diverse range of populations in Asia. In cases where it was necessary to look at evidence generated outside Asia, the expert panel used their clinical experience and expertise to analyze the data in the context of hypertension management in their region.

3 | RESULTS

The expert panel identified key items in relation to ABPM for discussion and generated consensus statements. These statements, their recommendations, and relevant supporting literature are discussed below and summarized in Consensus Tables A1-A11. Classification of recommendations and levels of evidence are shown in Table 1.

3.1 | Advantages and limitations of ABPM vs office and home BP in clinical practice

Ambulatory blood pressure monitoring provides several pieces of information that cannot be obtained from other methods of BP measurement (Consensus Table A1). These include a greater number of readings, the ability to estimate mean 24-hour BP, assessment of BP variability (BPV; particularly short-term variability), and better prediction of cardiovascular morbidity and mortaliy.[17] In addition, the readings obtained relate to an individual's BP in their usual daily environment, providing an indication of the effects of environmental and emotional factors on BP.[17,25] ABPM also appears useful for detecting ambulatory episodes of hypotension.[26,27] The characteristics of ABPM compared with HBPM and office-based BP measurement are shown in Table 2.

A number of studies have shown that 24-hour ambulatory BP correlates better with cardiovascular outcomes than office BP. In the Systolic Hypertension in Europe (Syst-Eur) trial of untreated elderly patients with isolated systolic hypertension, ambulatory systolic BP (SBP) provided prognostic information on cardiovascular risk that was additional to that provided by clinic BP values.[28] In a general population from Ohasama, Japan, ambulatory BP values, especially daytime BP, were a stronger predictor of stroke risk than clinic BP.[29] In the same population, both daytime and nighttime ambulatory BP values were closely associated with the risk of silent cerebrovascular lesions (detected on magnetic resonance imaging).[30]

The information obtained from ABPM is complementary to that generated by HBPM, and rational combination of these two approaches in clinical practice is recommended.[17,18,23] Cost (including reimbursement) and accessibility are potential issues that could limit the use of ABPM in some settings and/or countries,[31-33] although longer term savings are likely to offset the short-term costs of ABPM use.[17] ABPM can be inconvenient for patients so acceptability is also potentially problematic.[32,33] In addition, issues with the reliability of ABPM devices have been raised.[31] Cuff inflation during ABPM is associated with some discomfort, but this does not appear to increase heart rate.[34] ABPM use needs to be standardized to improve reproducibility.

TABLE 1 Classes of recommendation and levels of evidence

Classes of recommendations	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective (is recommended/is indicated)
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy (should be considered)
Class IIb	Usefulness/efficacy is less well established by evidence/opinion (may be considered)
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful (is not recommended)
Levels of evidence	
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large nonrandomized studies
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

3.2 | Measurement schedule and assessment of ABPM parameters

ABPM can be complex for patients, and adequate time is needed to provide appropriate and thorough education, including informing patients that cuff inflation might be associated with some discomfort (Consensus Table A2).[17] The use of an ABPM device that has been validated against accepted international standards, with associated software providing the data of interest, is recommended.[17] This should at least include presentation of all BP readings showing daytime and nighttime windows with an indication of normal BP, average SBP, diastolic BP (DBP) and heart rate, the percentage decline in nocturnal SBP and DBP, and summary statistics for time-weighted average SBP, DBP and heart rate for the 24-hour period, daytime, and nighttime, with standard deviations and number of valid BP readings.[17]

To obtain satisfactory ABPM data, the use of the non-dominant arm is preferred and an appropriate cuff should be provided.[17] Measurements should be taken every 15-30 minutes during the day and every 30-60 minutes at night, the ABPM recording needs to provide a minimum of 20 valid daytime and at least 7 valid nighttime measurements, and at least 70% of the expected 24-hour readings need to be valid. Collection of ABPM data on a normal workday (rather than a weekend or rest day) will provide a more typical BP profile.[25]

TABLE 2 Characteristics of ABPM, HBPM, and office BP

	Clinic/office BP	HBPM	ABPM
Measurement			
Frequency	Low	High	High
Standardization	Possible	Possible	Automatic
Teaching to whom	Clinician	Patient	Clinician
Reproducibility	Poor	Best	Good
White-coat effect	Not identifiable*	Identifiable	Identifiable
Masked effect	Not identifiable	Identifiable	Identifiable
Evaluation of BPV			
Seasonal	Possible	Possible	Impossible
Day-by-day	Impossible**	Possible	Impossible
Diurnal	Impossible	Possible#	Possible
Nighttime/sleep	Impossible	Possible##	Possible
Positional	Possible	Possible	Impossible
Short-term	Impossible	Impossible	Possible

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, BP variability; HBPM, home blood pressure monitoring.
*Partly identifiable if automated office BP monitoring is used.
**Possible using community BP measurement.
#Morning-evening difference.
##Using automated measurement.

Key 24-hour ambulatory BP values include 24-hour BP, daytime BP, nighttime BP, and morning BP (Table 3, Figure 1). Classification of daytime (awake) and nighttime (sleep) periods can be made based on diary cards completed by patients or using arbitrary 24-hour clock-based definitions (Table 3, Figure 1). The diary card-based approach is preferable because the use of arbitrary definitions does not account for inter-individual variation in bedtime and time spent in bed, and the 24-hour clock-based definitions are only reliable in individuals who go to bed and arise within well-defined periods.[35] This means that important data on the white-coat window, the early phase of nighttime sleep where dipping might be most marked, and the early morning BP surge might be missed.

3.3 | Definition of ABPM hypertension and BP goals

ABPM provides information on a number of different BP indices, including 24-hour, morning, daytime, and nighttime BP (Figure 1; Consensus Table A3). Guidelines recommend the use of out-of-office BP monitoring, including ABPM, to facilitate the diagnosis of hypertension, including detection of white-coat hypertension (WCH) and masked hypertension (MH).[13,16,18-23,36-38] ABPM is the gold standard for diagnosing hypertension and assessment of 24-hour BP, and has better sensitivity and specificity than either clinic or home BP measurements for the diagnosis of hypertension.[39]

3.3.1 | Thresholds for defining hypertension and monitoring response to treatment

ABPM thresholds for diagnosing hypertension and defining achievement of BP control during antihypertensive therapy have been defined (Consensus Table A3). Absolute values for ambulatory BP thresholds are lower than those for clinic or office BP (Table 4). Thresholds including a 24-hour average of ≥130/80 mm Hg, daytime average of ≥135/85 mm Hg, and nighttime average of ≥120/70 mm Hg are widely accepted and are supported by outcome

TABLE 3 Diary- and 24-h clock-based definitions of morning and nocturnal blood pressure parameters

	Diary-based definition	24-h clock-based definition
24-h BP	Average of readings over 24 h	Average of readings over 24 h
Daytime BP	Average of daytime readings from arising to going to bed	Average of daytime readings between 09:00 h and 21:00 h
Nighttime BP parameters		
Nighttime BP	Average of nighttime readings from going to bed to arising	Average of nighttime readings from 01:00 h to 06:00 h
Average peak nighttime SBP	Average of 3 highest nighttime SBP readings from going to bed to arising	Average of 3 highest nighttime SBP readings from 01:00 h to 06:00 h
Maximum nighttime SBP	Maximum nighttime SBP reading from going to bed to arising	Maximum nighttime SBP reading from 01:00 h to 06:00 h
Minimum nighttime SBP	Minimum nighttime SBP reading from going to bed to arising	Minimum nighttime SBP reading from 01:00 h to 06:00 h
Moving lowest nighttime SBP	Lowest 1-h moving average of consecutive SBP readings from going to bed to arising	Lowest 1-h moving average of consecutive SBP readings from 01:00 h to 06:00 h
Prewakening nighttime SBP	Average of nighttime SBP readings in the 2 h before arising	
Nighttime BP dipping parameters		
Nighttime dipping (%)	=(1 minus average nighttime SBP/average daytime SBP) × 100	
Subgroup classification based on nighttime SBP dipping (%)	=Extreme-dipper ≧20%; Dipper <20%, ≧10%; Non-dipper <10%, ≧0%; Riser <0%	
Morning BP parameters		
Morning BP	Average of readings in the 2 h after arising	Average of readings between 07:00 h and 09:00 h
Moving peak morning SBP	Highest 1-h moving average of consecutive SBP readings in the 2 h after arising	Highest 1-h moving average of consecutive SBP readings between 06:00 h and 10:00 h
Maximum morning SBP	Maximum morning SBP reading in the 2 h after arising	Maximum morning SBP reading between 06:00 h and 10:00 h
Minimum morning SBP		Minimum morning SBP reading between 05:00 h and 09:00 h before maximum morning SBP
Moving lowest preawakening morning SBP		Lowest 1-h moving average of consecutive SBP readings between 05:00 h and 09:00 h before moving peak morning SBP

Abbreviations: BP, blood pressure; SBP, systolic blood pressure.

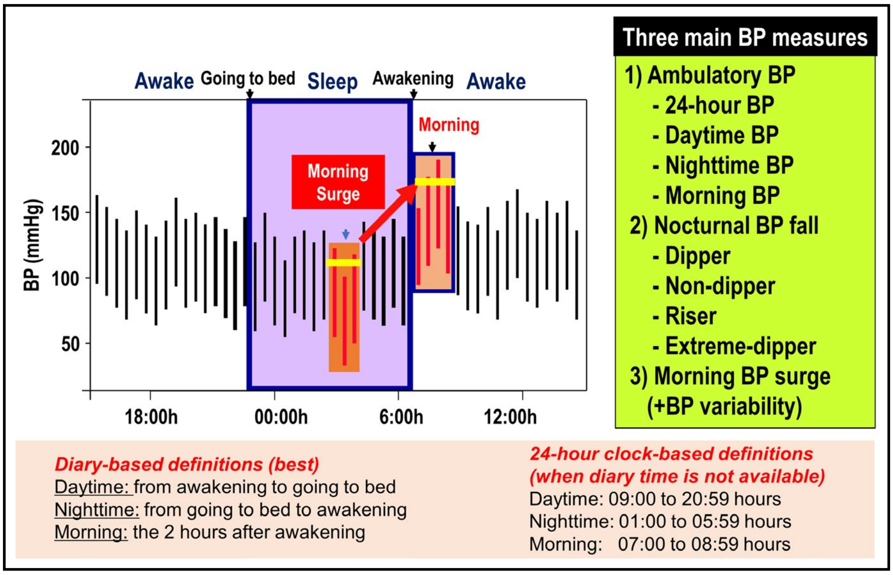

FIGURE 1 Blood pressure measures evaluated by ambulatory blood pressure monitoring. ABPM, ambulatory blood pressure monitoring; BP, blood pressure (adapted from Kario et al[114] with permission)

data.[23] More stringent thresholds are recommended in the most recent US guidelines (average daytime and morning BP thresholds are slightly higher, whereas thresholds for nighttime BP are lower).[22] However, the predictive value of these levels needs to be confirmed in future outcome studies.

The definition of BP control can vary, with lower thresholds defined to provide strict control of BP (Consensus Table A3). It is important to know whether prescribed treatment has restored BP to within the normal range throughout the 24-hour treatment period, and the only way to reliably achieve this is by repeated ABPM. Once BP control has been achieved and documented, periodic reassessment using ABPM will ensure the maintenance of 24-hour BP control.

3.3.2 | White-coat hypertension

The use of ABPM allows identification of patients who have WCH (elevated office BP and normal out-of-office BP; Figure 2). European recommendations suggest that individuals with suspected WCH should have the diagnosis confirmed using ABPM within 3-6 months after elevated office BP is detected, with follow-up ABPM performed annually to ensure that progression to sustained hypertension is detected.[17] In contrast, the Canadian diagnostic algorithm recommends performing HBPM or ABPM after the first clinic visit so that patients with WCH can be identified early.[40] Accurate diagnosis of WCH is important to avoid the costs and potential side effects associated with unnecessary antihypertensive pharmacotherapy. ABPM data showing a normotensive dip in a patient with WCH are shown in Figure A1. Both this and a normal pattern (Figure A2) show normal diurnal BP rhythm with a nighttime BP fall of 10%-19% compared with daytime BP.

3.3.3 | Masked hypertension

Masked hypertension is defined as a normal office BP and an elevated BP on out-of-office readings (Figure 2). ABPM has been described as the first-choice diagnostic method for detecting MH.[41] In individuals with normal office BP, MH could be characterized by elevated morning, daytime, and/or nighttime BP on ABPM (Figure 3). However, given that only about 10%-20% of patients with normotension based on office BP have MH,[42] referral of all those with normal office BP for ABPM is not practical. It is therefore suggested that the use of ABPM should be targeted to patient groups more likely to have MH, including males, older individuals, smokers, and those with a high body mass index (BMI), diabetes mellitus, or high serum cholesterol levels.[43] According to the latest US guidelines, adults with untreated office BP values consistently between 120/75 and 129/79 mm Hg are those who should be referred for out-of-office BP screening.[22] Identification of MH is important because of the increased risk of cardiovascular disease and target organ damage that accompanies this form of hypertension.[44-46]

3.4 | Clinical indications for ABPM

ABPM is considered the state-of-the art technology for BP measurement, and its use is endorsed by major international guidelines for North America,[22,37,47] Europe,[16,17,23] Japan,[21] China,[48] and Taiwan (Consensus Table A4).[13] ABPM plays a key role in the diagnosis and management of hypertension. It should be performed in individuals who show unstable and/or variable BP on office or home measurements because these patients are more likely to have WCH or MH.[17] In addition, unstable BP could also indicate poor control during antihypertensive therapy.[17] The use of ABPM in patients with resistant hypertension allows categorization of patients as having true resistance rather than white-coat resistance (seen in up to one-third of patients with resistant hypertension based on office BP alone[49,50]), allowing appropriate targeting of additional therapeutic interventions. Although there are some regional variations in specific recommendations (see Section 12), key indications for the use of ABPM are summarized in Table 5.

TABLE 4 Ambulatory blood pressure values corresponding to clinic measurements

Clinic BP (mm Hg)	Ambulatory BP (mm Hg) Daytime	Nighttime	24-h	Morning
120/80	120/80	100/65	115/75	120/80
130/80	130/80	110/65	125/75	130/80
140/90*	135/85*	120/70*	130/80*	135/85*
160/100	145/90	140/85	145/90	145/90

Abbreviation: BP, blood pressure.
*Pathologic threshold.

3.5 | Assessment and definition of disrupted diurnal BP pattern

Although there has been a tendency for guidelines to focus on ABPM daytime pressures, BP reflects the hemodynamic state and is not a static phenomenon (Consensus Table A5). Instead, there are both short-term and long-term variations that result from neurohumoral influences, environmental factors, and patient behavior (Figure 4). The importance of different BP profiles and BPV is increasingly being recognized, and the importance of achieving adequate reductions in BP throughout the 24-hour period cannot be overemphasized. Physiologically, there is circadian variation in BP, allowing physiological adaptability. Blood pressure is usually higher during the day (or periods of wakefulness) and lower at night (or periods of sleep). Extreme BPV could result in large dynamic surges that have the potential to trigger adverse cardiovascular events (the resonance hypothesis) and the risk of these events is exaggerated in high-risk patients with vascular disease.[51]

Nighttime (or nocturnal) BP is not affected by environmental factors in the same way that waking BP measurements are. It may therefore provide the most accurate representation of the BP phenotype in individual patients.[36] ABPM is the method of choice for evaluation of nighttime BP. Definitions of nighttime BP dipping parameters are shown in Table 3. The expected physiological fall in nighttime BP is ≧10% (dipping). ABPM data for a hypertensive dipper (normal diurnal variation) with an appropriate fall in nighttime BP (<20%, ≧10%) are shown in Figure A3. A reduction of <10% in BP at night is defined as non-dipping. Figure A4 shows a non-dipper ABPM pattern, with a reduced nighttime BP fall (10%, ≧0%). Extreme dipping (Figure A5) refers to patients who show a marked nocturnal fall (≧20%) in SBP and/or DBP, or have a night/day SBP or DBP ratio of <0.8.[18] Extreme dipping has been associated with a significant increase in the risk of intracerebral hemorrhage compared to patients with a physiological fall in nighttime BP.[52] Patients with a riser, or reverse dipping, pattern show an increase in BP during sleeping hours to levels that may be higher than those during the day.[53] The ABPM profile for a riser pattern with higher nighttime vs daytime BP is shown in Figure A6. Nocturnal hypertension (BP ≥ 120/70 mm Hg) may indicate the presence of comorbidities such as obstructive sleep apnea (OSA), and the riser pattern of nighttime BP is associated with a particularly poor prognosis with respect to the occurrence of stroke and cardiac events.[54]

3.6 | Assessment and definition of disrupted short-term blood pressure variability

Put simply, BPV refers to variations in BP over time (Consensus Table A6). There are a number of different components to BPV, including diurnal or circadian (as described above), short-term, and long-term variations in BP. Factors affecting BPV include genetics, mechanical forces generated during ventilation, local vasomotor phenomena, sympathetic nervous system activity, electrolytes neurohumoral factors, physical activity, arterial wall thickness, baroreflex mechanisms, time of day, seasonal influences, and possibly also environmental factors.[55] Short-term BP is primarily determined by physiological regulation of the neural network. Impaired baroreflex secondary to increased central sympathetic tone and/or vascular stiffness is a key determinant of disrupted short-term BPV.[56]

One important component of short-term BPV is the morning BP surge, defined as the difference between morning BP measured 2 hours after waking and the lowest nighttime BP (Table 3). This can only be detected using ABPM. The synergistic resonance hypothesis suggests that the early morning BP surge can be potentiated by a combination of factors, including beat-to-beat, visit-to-visit, orthostatic, diurnal, seasonal, annual, and physical or psychological stress-induced BPV.[51] ABPM-derived measures of short-term BPV include the standard deviation (SD), coefficient of variation (CV), average real variability (ARV), variability independent of the mean (VIM) for daytime BP, nighttime BP, weighted SD of 24-hour BP values, and peak and trough values for daytime and nighttime BP.

3.7 | 24-hour BP characteristics of specific diseases

Sleep is an important determinant of the diurnal variation in BP, with BP usually decreasing during sleep (Consensus Table A7). Patients with OSA often have disrupted sleep, and the prevalence of arterial hypertension and MH in this group is high.[57] Common ABPM findings in patients with OSA include non-dipping profile, morning BP surge, and increased BPV.[58,59] Correlations between the evening-to-morning BP difference and the severity of OSA have been reported.[60-67] Increasing apnea-hypopnea index (AHI) or oxygen desaturation index (ODI) appear to be significant predictors of a non-dipping ambulatory BP profile,[65,68-72] while arousals may be a determinant of nocturnal BP and the 24-hour BP profile.[73,74] Thus, individual ambulatory and BPV characteristics need to be evaluated

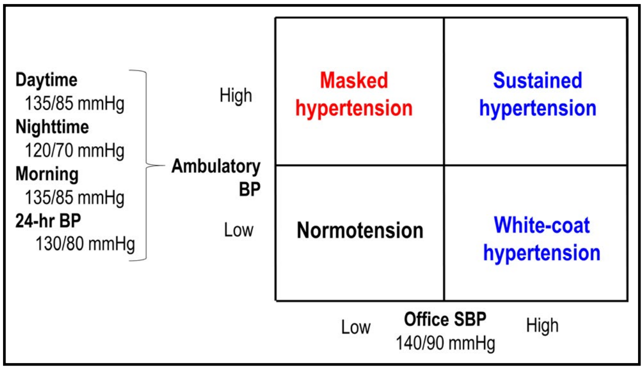

FIGURE 2 Hypertension classifications based on office and ambulatory blood pressure

using ABPM and incorporated into the management of patients with OSA. Furthermore, OSA should be considered and investigated in patients with resistant morning or nocturnal hypertension, particularly in the setting of coexisting target organ damage.[58]

Hypertension is an important risk factor for cardiovascular disease in patients with diabetes mellitus. Patients with diabetes show a high prevalence of alterations in ABPM.[75] Mean 24-hour BP values are higher in patients with type 1 diabetes mellitus compared to controls without diabetes.[76,77] In addition, non-dipping is common in diabetes[75,76,78,79] and this is not detected on office BP measurement, meaning that ABPM has an important role. Masked hypertension is also more common in patients with vs without diabetes and appears to increase the risk of target organ damage.[80]

Patients with chronic kidney disease (CKD) have a high prevalence of MH, which is a significant predictor of progression to end-stage renal disease and total mortality.[81-84] Abnormal ABPM findings in CKD include nocturnal non-dipping[85] and increased BPV,[85,86] both of which increase in prevalence as the severity of CKD increases.[87] In addition, non-dipping in patients with CKD has been associated with the rate of decline in renal function.[88,89] Various other underlying causes of secondary hypertension, including renovascular hypertension, primary aldosteronism, Cushing syndrome, and pheochromocytoma, are associated with a higher prevalence of non-dipper pattern and nocturnal hypertension.[90,91]

Specific agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and Kanzo [liquorice] increase the circulating volume, resulting in a non-dipping pattern and nocturnal hypertension.[92-94]

3.8 | Asian characteristics of the 24-hour BP profile

There are a number of important and clinically relevant features of hypertension in Asian populations (Consensus Table A8). In terms of predisposing factors, both salt sensitivity and salt intake are higher, and pre-hypertension develops at a lower BMI and with smaller BMI increments in Asians compared with European populations.[9,10] In addition, Asians are likely to have a genetic predisposition to salt-sensitive gene polymorphism of the renin-angiotensin system.[10]

The prevalence of masked (uncontrolled) hypertension, excessive morning BP surge and morning hypertension, and nocturnal hypertension is higher in Asians than in Europeans (Table 6).[56,95-99] Japanese patients with resistant hypertension have significantly higher morning SBP, moving peak morning SBP, morning dynamic surge, and night dynamic surge compared with Black and White Americans, highlighting the presence of important ethnic differences.[96] In another study, the sleep-trough morning BP surge in Japanese patients with untreated hypertension was significantly higher than that in similar patients from Europe, independent of age, 24-hour BP and lowest nocturnal BP (40.1 vs 23.0 mm Hg; $P < .001$).[95] This may be due to the strong link between sympathetic nervous system activity and salt intake,[100] and the fact that dietary salt intake is higher in Asian than in Western populations. In addition, data from the international Ambulatory Blood Pressure Registry: Telemonitoring of Hypertension and Cardiovascular Risk Project (ARTEMIS) showed that MH and masked uncontrolled hypertension were diagnosed more often in Asia than in any other region.[98] This

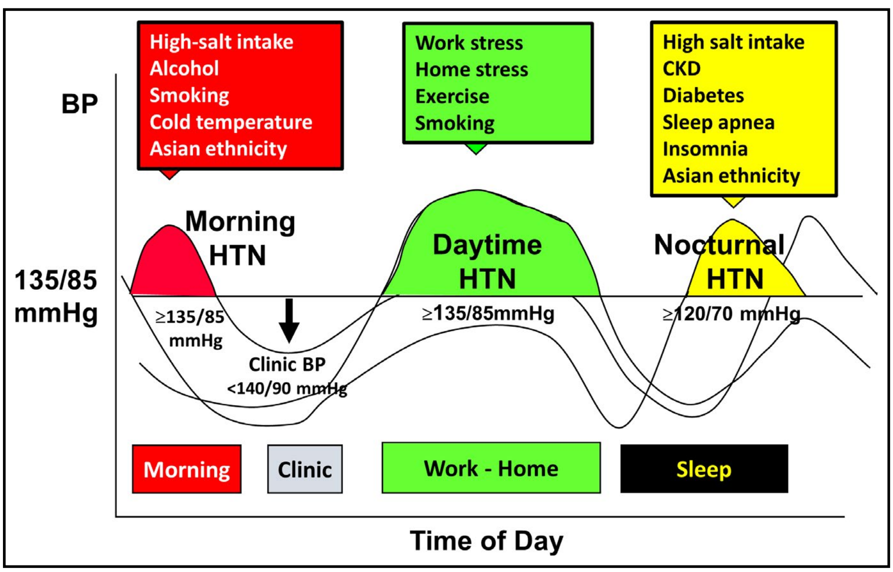

FIGURE 3 Different types of masked hypertension and contributing factors. BP, blood pressure; CKD, chronic kidney disease; HTN, hypertension (modified from Kario[102])

TABLE 5 Clinical indications for ABPM in addition to HBPM

1. Increased home BPV and abnormal 24-h BP patterns	Detected by determination of standard deviation, coefficient of variation, average real variability, morning-evening difference, or peak home BP
2. Advanced target organ damage	Including left ventricular hypertrophy, advanced vascular disease, heart failure with preserved ejection fraction, chronic kidney disease, cognitive dysfunction
3. Suspected masked hypertension	Nocturnal hypertension (related to obstructive sleep apnea, diabetes and/or chronic kidney disease) or daytime hypertension (related to stress or smoking habit)
4. Suspected white-coat hypertension	To exclude the presence of persistent hypertension and avoid unnecessary treatment
5. Secondary hypertension	Related to other conditions, including obstructive sleep apnea, chronic kidney disease, renovascular hypertension, and primary aldosteronism
6. Monitoring antihypertensive therapy	Assessment of 24-h BP control, and identification of treatment resistance
7. Drug-resistant hypertension	Persistent hypertension despite treatment with three or more antihypertensive drugs

may be due to a lower BMI in Asian vs Western populations.[101] All of these different Asia-specific features of hypertension can be detected using ABPM, highlighting the importance of this technique in Asian populations.

The complications of hypertension also show ethnic variations. In Western subjects, coronary heart disease (CHD) is a more common complication of hypertension, whereas stroke occurs at a higher rate than CHD in Asians.[8,12] The development of both stroke and non-ischemic heart failure is closely related to the presence of hypertension, and both of these comorbidities are more common in Asian than in Western countries.[4,5] In addition, the slope of the relationship between increasing BP and cardiovascular events, especially stroke, is steeper in Asians than in Westerners.[4,102-104] Furthermore, data from the Asia Pacific Cohort Studies Collaboration showed that there was a stronger relationship between BP and cardiovascular disease in Asian patients than in those from Australia and New Zealand.[7,11]

Strict BP control throughout the 24-hour period is important for all patients, but this is particularly the case in Asia.[3] Given the greater effect of BP reductions on stroke and heart failure vs CHD,[105] and the higher rate of these events in Asians,[8,12] the beneficial effects of BP lowering may be more marked in Asian compared with Western populations.[4] Treatment with a long-acting calcium channel blocker (CCB) has been shown to be effective for lowering office, home morning, and 24-hour ambulatory BP, and reducing exaggerated BPV, independently of salt intake and salt sensitivity.[106-109] This approach is therefore well suited to the characteristics of Asian patients with hypertension. The use of ABPM is required to evaluate the effects of antihypertensive treatment on 24-hour BP and the BPV profile.

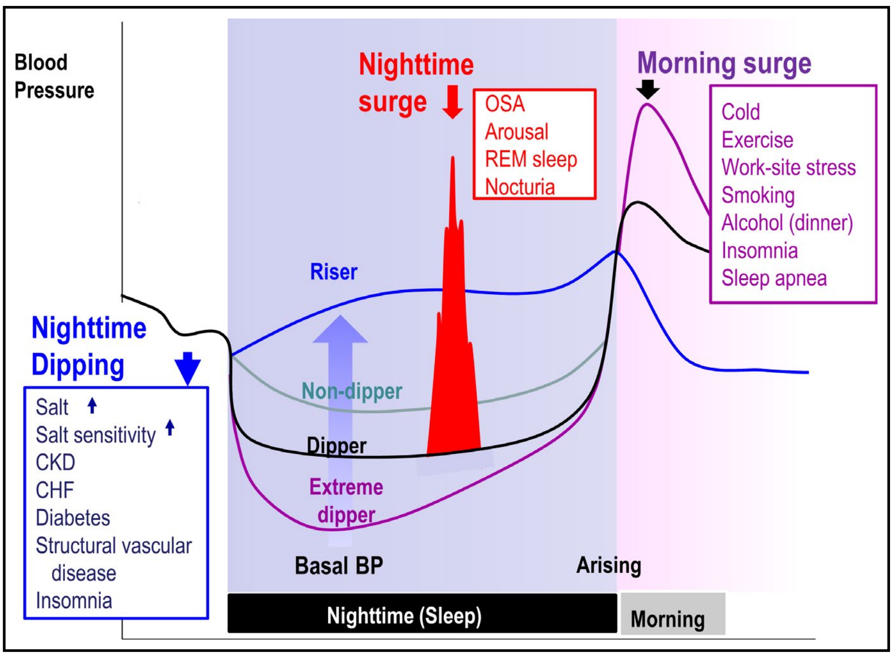

FIGURE 4 Influences on nocturnal and morning blood pressure, and different classifications of nighttime dipping. BP, blood pressure (reproduced from Kario[90] with permission)

TABLE 6 Ethnic differences in the prevalence of isolated nocturnal hypertension[97]

	Proportion of patients with isolated hypertension (%)	
	Nighttime	Daytime
Asian		
Chinese (n = 677)	10.9	4.9
Japanese (n = 1038)	10.5	6.0
Non-Asian		
Eastern European (n = 854)	7.9	13.9
Western European (n = 3268)	6.0	9.1
South African (n = 201)	10.2	6.6

Note: Isolated nighttime hypertension = nighttime blood pressure ≥ 120/70 mm Hg and daytime blood pressure < 135/85 mm Hg; Isolated daytime hypertension = daytime blood pressure ≥ 135/85 mm Hg and nighttime blood pressure < 120/70 mm Hg.

3.9 | ABPM parameters predicting cardiovascular outcomes

The risk of hypertensive cardiovascular complications appears to correlate better with 24-hour BP measured using ABPM than with office BP measurements, both in the general population and in the elderly (Consensus Table A8).[110-112] Literature supporting the relationship between various ABPM parameters and cardiovascular risk or target organ damage is summarized in the next two sections and detailed in Table 7.

3.9.1 | Morning BP surge

Early morning BP surge is associated with an increased risk of cardiovascular and cerebrovascular adverse events, especially hemorrhagic stroke.[52,95,113-118] In a study of 340 ABPM subjects from China, the proportion of those showing an early morning BP surge was greater among individuals with hypertension vs normotension, and this surge was significantly and independently associated with the occurrence of stroke and cardiovascular events.[119] Japanese ABPM data from the Jichi Medical University School of Medicine (JMS-ABPM study) showed that the incidence of stroke events in the morning hours was higher in subjects with vs without an exaggerated morning BP surge, and persisted after adjustment for age, 24-hour BP, and nighttime dipping status.[114] The International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO), including 5645 subjects from 8 populations, provided definitive data showing that both sleep-trough and preawaking morning BP surges were independent risk factors for total mortality and cardiovascular events.[120] Similar to the JMS-ABPM study, IDACO data showed that individuals with morning BP surge values in the top decile were at risk of mortality or cardiovascular events after controlling for covariates including age and 24-hour BP. A recent long-term prospective study of more than 2000 subjects with ABPM data followed for a median of 20 years showed that the sleep-trough morning surge rate (defined as the slope of linear regression of sequential SBP values against time intervals within the morning surge period) was an independent predictor of cardiovascular death (hazard ratio 2.61) whereas the amplitude of the morning surge was not significantly associated with cardiovascular mortality risk.[121]

In a meta-analysis of seven prospective studies evaluating morning surge in a total of 14 133 patients over a mean follow-up of 7.1 years, excess sleep-trough morning surge was a strong predictor of future all-cause mortality (relative risk 1.29; $P = .001$).[122] Another meta-analysis of 17 studies did not find any clear evidence for the impact of preawaking morning BP surge on prognosis. However, using a continuous scale, which has more power to detect an association, there was evidence that a 10 mm Hg increase in morning surge was related to an increased risk of stroke (hazard ratio 1.11, 95% confidence interval 1.03-1.20).[123]

3.9.2 | Non-dipping

Non-dipping is particularly common in patients with diabetes mellitus (prevalence of up to 30%)[54,78] and has been linked to increased risk of target organ damage, stroke, cardiovascular events, and mortality in some studies.[78,124] Although a large number of studies, conducted in the general population and in patients with hypertension, have investigated the prognostic impact of non-dipping status, results have not been consistent. This is probably due to a number of issues, including the poor reproducibility of dipping status,[125] contribution of environmental, genetic, seasonal and positional factors,[126,127] sleep quality,[128,129] the time of dosing and duration of action of antihypertensive therapy,[130] and others.[131,132] In addition, differences in study design, control for confounding factors, and how non-dipping was defined between studies are an issue. Another potential confounding variable is sleep duration, because non-dippers with short sleep duration have been shown to have the worst cardiovascular prognosis.[133]

In the study where non-dipping was first defined, patients with a non-dipping BP profile had a significantly higher stroke risk.[134] The results of some subsequent studies support a link between non-dipping status (elevated nocturnal BP) and a higher rate of cardiovascular events,[28,130,135-154] but others failed to find such an association.[155-160]

In a large meta-analysis of data from prospective clinical studies including 23 856 patients with hypertension and 9641 subjects from the general population, dipping status and the night/day BP ratio were significant predictors of outcome (total mortality and/or cardiovascular events) after adjustment for the 24-hour BP and other confounding factors.[161] However, adding dipping status and the night/day BP ratio to the model after 24-hour BP only made a small additional contribution to explaining variance in mortality and cardiovascular outcomes.[161]

TABLE 7 Summary of Asian studies investigating the effects of ABPM parameters on cardiovascular prognosis and target organ damage

Author, year (study name)	Design; population	Total subjects (n)	Follow-up	Main findings
Cardiovascular prognosis				
Cheng et al 2017[121]	Prospective	2020	Median 19.7 y	High sleep-trough MS rate was significantly associated with increased all-cause mortality risk (HR 1.666, 95% CI 1.185-2.341) and CV mortality (HR 2.608, 95% CI 1.554-4.375), independent of age, sex, BMI, smoking, alcohol, LDL cholesterol, 24-h SBP, night:day SBP ratio, and antihypertensive treatment
Hsu et al 2016[165]	Prospective; Community-based population of pts with untreated HTN or normotension	1257	Median 20 y	In pts with HTN, high vs low ARVd was a significant predictor of CV mortality (HR 2.04, 95% CI 1.19-3.51) after adjustment for 24-h SBP and conventional risk factors; no such association was seen in normotensives
Luo et al 2013[119]	Retrospective case-control; Primary hypertension (2-wk washout of antihypertensives) or normotension	340	Unknown	The rate of morning surge in SBP was an independent determinant of MI (OR 1.266, 95% CI 1.153-1.389, $P < .001$) and stroke (OR 1.367, 95% CI 1.174-1.591, $P < .001$)
Shimizu et al 2011[176]	Prospective; Elderly hypertensives	514	Mean 41 m	The rate of silent cerebral infarcts was significantly higher in pts in the highest quartile of MS and an hs-CRP level above the median (OR 2.74, 95% CI 1.42-5.30) vs pts in lower quartiles of MS and with lower hs-CRP. The high MS, high hs-CRP group also had a significantly increased risk of clinical stroke events (HR 5.77, 95% CI 2.11-15.81), even after adjustment for confounding variables
Eguchi et al 2008[156]	Prospective; Asymptomatic pts with HTN, with or without diabetes	1268	Mean 50 m	24-h SBP was independently associated with CVD in patients with (HR 1.44, 95% CI 1.15-1.80; $P < .001$) and without (HR 1.32, 95% CI 1.10-1.58; $P = .001$) diabetes
Ishikawa et al 2008[147]	Prospective; Pts aged > 50 y with essential HTN	811	Mean 41 m	After adjustment for 24-h BP and covariates (including CKD), extreme dipping status remained significantly associated with the occurrence of CV events (HR 2.59, 95% CI 1.26-5.32; $P = .009$)
Metoki et al 2006[52] (Ohasama)	Prospective; General population	1430	Mean 10.4 y	Cerebral infarction risk was significantly higher in subjects with a ≥10% vs <10% nocturnal decline in BP ($P = .04$). Risk of cerebral hemorrhage was increased with a large morning pressor surge (≥25 mm Hg; $P = .04$), and intracerebral hemorrhage occurred more frequently in extreme dippers vs dippers ($P = .02$)
Nakano et al 2004[148]	Prospective; Pts with type 2 diabetes and no history of vascular disease	392	Mean 86 m	Nighttime SBP was a significant predictor of nonfatal vascular events (adjusted RR 1.03, 95% CI 1.10-1.06; $P = .041$)
Kario et al 2003[114]	Prospective; Elderly hypertensives	519	Mean 41 m	After adjustment for age and 24-h BP, RR of stroke in the MS vs non-MS group was 2.7 ($P = .04$); MS was significantly associated with stroke events independently of 24-h BP, nocturnal BP dipping status and baseline presence of silent infarct ($P = .008$)
Liu et al 2003[190]	Prospective; Hemodialysis pts	80	Mean 33 m	On Cox analysis, non-dipping was significantly associated with the occurrence of CV events (HR 2.46, 95% CI 1.02-5.92; $P = .038$) ad CV mortality (HR 9.62, 95% CI 1.23-75.42; $P = .031$)

(Continues)

TABLE 7 (Continued)

Author, year (study name)	Design; population	Total subjects (n)	Follow-up	Main findings
Ohkubo et al 2002[54] (Ohasama)	Prospective; General population (age ≥ 40 y)	1542	Mean 9.2 y	On average, each 5% reduction in the decline in nocturnal BP was associated with a ≈20% increase in the risk of CV mortality; this relationship was evident even when 24-h BP was within the normal range
Kario et al 2001[137]	Prospective; Elderly pts with sustained hypertension	575	Mean 41 m	Multiple silent cerebral infarct on brain MRI was seen in 53% of extreme dippers, 49% of reverse dippers, 41% of non-dippers and 29% of dippers. Corresponding values for stroke incidence were 12%, 22%, 7.6%, and 6.1%. Intracranial hemorrhage was more common in reverse dippers (29% of strokes) than in other subgroups (7.7% of strokes, $P = .04$)
Kikuya et al 2000[167] (Ohasama)	Prospective; General population (age ≥ 40 y)	1542	Mean 8.5 y	In a Cox proportional hazards model adjusted for potential confounders, there was a significant linear relationship between increasing daytime systolic, daytime diastolic and nighttime BPV and CV mortality; CV mortality risk was highest in subjects with daytime ambulatory systolic BPV was above the third quintile
Ohkubo et al 1997[153] (Ohasama)	Prospective; General population (age ≥ 40 y)	1542	Mean 5.1 y	Adjusted (for age, sex, smoking status, CVD history, use of antihypertensives, and nighttime BP) HR (95% CI) for CV mortality vs dippers were 2.43 (1.05-5.62) in non-dippers and 2.66 (1.03-6.87) in inverted dippers.
Target organ damage				
Cho et al 2018[203]	Cross-sectional; Ambulatory elderly pts with ≥1 CV risk factor (92% treated with antihypertensives)	232	–	Pts were divided into quartiles based on weighted SD of 24-h SBP. After adjustment for age and 24-h SBP, quartile 4 of weighted SD of BP had a lower MoCA-J score (indicating cognitive impairment) vs quartile 1 and 2 (15.4 vs 17.9; $P = .0001$)
Wei et al 2014[247]	Cross-sectional; Untreated pts referred for ABPM	1047	–	In fully adjusted multivariable models in older and younger pts (≥55 and <55 y, respectively), 24-h SBP was a significant predictor of target organ damage, including LVMI, UACR, and PWV
Kawai et al 2011[179]	Cross-sectional; Pts with or without HTN undergoing renal doppler ultrasound	194 (88 with ABPM)	–	Pts with a larger MS on ABPM had a significantly higher resistance index (RI) on renal doppler ultrasound vs other pts (0.73 ± 0.06 vs 0.70 ± 0.08; $P < .05$)
Nagai et al 2009[193]	Cross-sectional; Elderly hypertensives with ≥1 CV risk factor	55	–	In multiple linear regression analysis adjusted for age, gender and BMI, left insular cortex volume was significantly negatively associated with sleep SBP ($P < .01$) and positively with nocturnal SBP dipping ($P < .05$)
Nagai et al 2008[192]	Cross-sectional; Unmedicated elderly hypertensives with ≥1 CV risk factor	55	–	Nocturnal SBP dipping was significantly correlated with total brain matter volume (r-.323; $P = .02$) and Mini-Mental State Examination score ($r = 0.402$; $P = .002$). In multiple linear regression analysis adjusted for age, sex and BMI, sleep SBP ($P = .009$) was more significantly negatively associated with total brain matter volume than either 24-h ($P = .035$) or awake ($P = .020$) SBP
Hoshide et al 2007[191]	Cross-sectional; Adults undergoing ABPM	165	–	Multiple regression analysis showed that nocturnal SBP was independently associated with IMT ($\beta = .10$, $P < .05$) and RWT ($\beta = .28$, $P < .001$) adjusted for by age, male gender, BMI and self-measured home SBP

(Continues)

TABLE 7 (Continued)

Author, year (study name)	Design; population	Total subjects (n)	Follow-up	Main findings
Li et al 2007[99]	Cross-sectional, population study; Subjects aged ≥12 y	733	–	Subjects with isolated nocturnal HTN showed significantly increased arterial stiffness (based on 4 different measures) vs subjects with ambulatory normotension (all $P < .05$; adjusted for sex, age, height and pulse rate)
Sakakura et al 2007[202]	Cross-sectional; Stable chronic disease pts (including HTN) aged 61-79 or ≥80 y)	202	–	Exaggerated ambulatory BPV was related to cognitive dysfunction in the elderly (especially the very elderly), and was related to lower QOL in the younger elderly
Kario et al 2004[177]	Cross-sectional; Elderly hypertensives	98	≤11 wk	Although age, clinic BP and 24-h BP were similar, pts with vs without MS had a significantly higher prevalence of LV hypertrophy, multiple silent cerebral infarcts, and number of silent cerebral infarcts (all $P < .05$). After adjustment for possible confounders (age, sex, BMI, smoking, hyperlipidemia, duration of HTN and dose of doxazosin), both MS ($P < .05$) and alpha-adrenergic-related MS ($P < .001$) were significantly associated with the number of silent cerebral infarcts
Hoshide et al 2003[183]	Cross-sectional; Normotensives	74	–	Non-dippers vs dippers had higher LV mass index ($P < .05$), relative wall thickness ($P < .01$) and levels of atrial ($P < .01$) and brain ($P < .05$) natriuretic peptides, and a greater prevalence of concentric hypertrophy ($P < .05$)
Watanabe et al 1996[197]	Cross-sectional, epidemiological survey; Untreated subjects (aged > 55 y)	70	–	Women, but not men, showed a significant positive correlation between the amplitude or the rate of fall in nocturnal BP and the extent of periventricular hyperintensity on MRI (silent cerebral lesions)
Kario et al 1996[198]	Cross-sectional; Hypertensive out-pts aged ≥60 y (untreated for ≥1 m)	131	–	In pts with sustained HTN (n = 100), the extent of silent cerebrovascular damage was greater in extreme dippers and non-dippers than in those with a dipping pattern; there was a J-shaped relationship between nocturnal BP fall and brain MRI findings

Abbreviations: ABPM, ambulatory BP monitoring; ARTEMIS, International Ambulatory Blood Pressure Registry: Telemonitoring of Hypertension and Cardiovascular Risk Project; ARVd, average real variability in diastolic BP; ARVs, average real variability in systolic BP; BMI, body mass index; BP, blood pressure; BPV, BP variability; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; IHD, ischemic heart disease; IMT, intima-media thickness; LV, left ventricular; LVMI, left ventricular mass index; m, months; MI, myocardial infarction; MoCA-J, Montreal Cognitive Assessment—Japanese version; MRI, magnetic resonance imaging; MS, morning surge; OR, odds ratio; pts, patients; PWV, pulse wave velocity; RR, relative risk; RWT, relative wall thickness; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio; wk, weeks; y, years.

3.9.3 | Riser pattern/nocturnal hypertension

Reduction of nocturnal hypertension is an important part of achieving optimal 24-hour BP management and reducing or eliminating cardiovascular events.[56] In addition, nocturnal BP may be the most reproducible and reliable ABPM parameter for risk stratification.[36] The most recent analysis, based on the IDACO database, suggested that nocturnal SBP was a better predictor of cardiovascular risk (especially stroke risk) than dipping status or nocturnal SBP dipping ratio, possibly due to the good reproducibility of nighttime BP and the poor reproducibility of measures of dipping status. The authors concluded that nocturnal BP might be the most appropriate of the three parameters for risk stratification.[160] This is consistent with the findings of the Systolic Hypertension in Europe trial, in which nighttime SBP was the most accurate predictor of cardiovascular endpoints.[28] The riser pattern of nighttime BP is associated with a particularly poor prognosis with respect to the occurrence of stroke and cardiac events.[54]

The negative impact of nocturnal hypertension on cardiovascular risk is particularly marked in the presence of diabetes mellitus. In a prospective study of hypertensive patients, the increase in cardiovascular risk associated with nocturnal hypertension vs normotension (nocturnal SBP ≥ 135 mm Hg vs <120 mm Hg) was 10.8-fold in patients with diabetes compared with 2.7-fold in those without diabetes.[156]

3.9.4 | Extreme dipping

Extreme dipping (characterized by a ≧20% fall in nocturnal BP on ABPM) has been associated with a number of adverse outcomes, especially cerebrovascular events. Data from the JMS-ABPM study showed that elderly hypertensive patients with an extreme-dipper pattern were at increased risk of future clinical stroke events.[137] Similarly, another study showed that extreme dipping was associated with a significant increase in the risk of intracerebral hemorrhage compared to patients with a physiological fall in nighttime BP.[52] In a meta-analysis of data from 17 312 patients with hypertension across three continents, the Ambulatory Blood pressure Collaboration in patients with Hypertension (ABC-H) found that an extreme-dipper pattern was significantly associated with cardiovascular events only in unmedicated patients.[162]

3.9.5 | Short-term BPV

Available evidence suggests that BPV is an important predictor of cardiovascular risk in patients with hypertension.[163] Therefore, reduction in BPV should be one of the goals of ABPM-directed antihypertensive treatment. Using ABPM in patients with hypertension, the risk of cardiovascular morbidity and mortality at 3-year follow-up was significantly higher in those with SBP variability of >15 vs ≤15 mm Hg (P < .01).[164] In hypertensive patients from Taiwan, reading-to-reading ARV in diastolic BP (ARVd) on ABPM was an independent predictor of cardiovascular mortality in patients with hypertension, after adjustment for conventional risk factors and both office and 24-hour SBP; similar (but weaker) associations were seen for ARV in SBP (ARVs).[165] The hemodynamic variable showing the most dominant independent association with ARV appears to be pulse wave reflection.[166] In the Ohasama study, which included 1542 individuals from a general Japanese population, those in the highest quintile for daytime SBP BPV (>18.8 mm Hg) had a significantly higher risk of cardiovascular death compared with subjects with SBP SD in the second quintile (11.5-13.9 mm Hg), and those in the highest quintile for nighttime BPV (>14.4 mm Hg) were at significantly higher risk of cardiovascular death compared to individuals with SBP BPV in the fourth quintile (11.8-14.4 mm Hg).[167] Although short-term BPV has been successfully used for risk stratification in population and cohort studies, its use in clinical practice is limited by a lack of accepted thresholds defining normal and pathologic short-term BPV.[17]

3.10 | ABPM parameters associated with target organ damage

3.10.1 | Morning surge

Markers of hypertensive heart disease, including increased left ventricular mass index (LVMI), left ventricular hypertrophy, and a lower A/E ratio (a measure of diastolic dysfunction), have all been associated with an exaggerated morning BP surge (Consensus Table A10).[113,168-170] Significant relationships have also been reported between increased morning BP surge and both increased carotid intima-media thickness (IMT) and microvascular dysfunction.[168,171,172] Vascular function, assessed using pulse wave velocity (PWV), has been shown to be impaired in patients with exaggerated morning BP surge.[173,174] Histologic data suggest that exaggerated morning BP surge accelerates the formation of atherosclerotic plaques and induces plaque instability as a result of vascular inflammation.[175] In the JMS-ABPM study, morning BP surge in the highest quartile was significantly correlated with levels of the inflammatory marker high-sensitivity C-reactive protein (hs-CRP).[114]

Asymptomatic cerebral infarcts are important surrogate markers for the occurrence of stroke, especially in the presence of increased CRP levels. In the JMS-ABPM study, a significantly higher proportion of patients with vs without exaggerated morning BP surge and hs-CRP levels above the median had asymptomatic cerebral infarcts on brain magnetic resonance imaging.[176] These silent cerebral infarcts appear to be most closely related to the component of exaggerated morning BP surge associated with alpha-adrenergic activity.[177]

Data on the role of morning BP surge in CKD are limited. One cross-sectional study in normotensive patients with newly diagnosed type 2 diabetes mellitus found that patients with microalbuminuria had significantly higher morning BP surge than patients without microalbuminuria,[178] although the correlation between increasing morning BP surge and albuminuria in another study was weak (r = .126; P < .05).[174] In addition, sleep-trough morning BP surge has been significantly associated with a higher resistive index (a marker of renal vascular resistance) in patients at risk of atherosclerosis.[179]

3.10.2 | Non-dipping

A number of studies have shown blunted nighttime BP dipping to be associated with target organ damage.[53,180-185] In untreated normotensive Japanese subjects, those with a blunted fall in nighttime BP demonstrated signs of cardiac overload vs those who showed a normal fall in nighttime BP.[137,183] A non-dipping nighttime BP pattern was associated with asymptomatic cerebrovascular disease in elderly hypertensive patients; both silent cerebral infarcts and deep white matter lesions were detected on brain magnetic resonance imaging.[53] Furthermore, kidney damage has been reported in patients with a non-dipping pattern of BP,[89,186-189] and a non-dipping BP pattern was shown to be an important predictor of cardiovascular events and mortality in patients with end-stage renal disease.[190]

3.10.3 | Riser pattern/nocturnal hypertension

In a Japanese study, patients with masked nocturnal hypertension (home BP < 135/85 mm Hg and ambulatory nocturnal BP ≥ 120/75 mm Hg) had greater IMT and relative wall thickness than normotensive individuals.[191] Elderly hypertensive non-dippers and risers have been shown to have atrophy of the brain and insular cortex.[192,193] In addition, both the non-dipper pattern and the nocturnal hypertension are significantly associated with cognitive dysfunction and slow walking speed in elderly subjects.[168] In a Chinese population study, subjects found to have isolated nocturnal hypertension on ABPM (nighttime BP ≥ 120/70 mm Hg) showed significantly increased arterial stiffness (central augmentation index, peripheral augmentation index, ambulatory arterial stiffness index, and brachial-ankle PWV) compared with normotensive subjects after adjustment for sex, age, height, and pulse rate (all $P < .05$).[99] Even when home BP is well controlled, nocturnal hypertension on ABPM (nighttime SBP ≥ 120 mm Hg) was associated with attenuated reduction in the UACR and increased levels of plasma B-type natriuretic peptide (BNP) compared with well-controlled nocturnal BP (SBP < 120 mm Hg).[194] This highlights the importance of ABPM in ensuring that adequate reduction in all BP parameters is achieved during antihypertensive therapy.

3.10.4 | Extreme dipping

Extreme dippers have been shown to have more advanced deep white matter lesions on brain magnetic resonance imaging, reduced cerebral blood flow and increased PWV.[195-198] In the CARDIA study of young normotensive subjects, extreme dippers, non-dippers and risers, defined by baseline ABPM, developed more advanced coronary calcification (detected by coronary computed tomography) during follow-up (≥10 years). Even after controlling for baseline covariates, the risk of having coronary calcium was four or more times greater in both extreme dippers and non-dippers/risers compared with normal dippers.[199]

3.10.5 | Short-term BPV

When mean 24-hour BP was similar, hypertensive patients with greater BPV had an increased LVMI compared to those with lower BP variability.[200] In another study, the development of early carotid atherosclerosis was significantly increased in patients with SBP variability of >15 vs ≤15 mm Hg ($P < .005$).[164] Circadian hyper-amplitude tension (CHAT; defined as circadian amplitude exceeding the upper 95% prediction limit for clinically healthy peers matched by gender, age and ethnicity) was associated with increased LVMI in an analysis of 2039 untreated patients with hypertension.[201] In the very elderly, an increase in ambulatory BPV has been shown to be significantly associated with cognitive dysfunction, assessed using the Mini-Mental State Examination.[202] Even when ambulatory BP was well controlled in another study of elderly patients (mean age 78 years), increased ambulatory BPV (assessed using the standard deviation of ambulatory SBP)—but not average ambulatory BP—was significantly associated with cognitive dysfunction assessed using the Japanese version of the Montreal Cognitive Assessment.[203]

3.11 | Antihypertensive treatment assessed by ABPM

In clinical practice, good BP control includes three components: reducing 24-hour BP, maintaining normal circadian rhythm (dipper type), and suppressing exaggerated BPV (especially the morning surge; Figure 5); ABPM has the ability to determine all of these important parameters and therefore has a role in monitoring the BP-lowering effects of lifestyle modifications and antihypertensive therapy (Consensus Table A10). For example, the use of ABPM showed that nutritional advice combined with salt restriction was associated with a significant reduction in 24-hour SBP in treated Japanese patients with hypertension.[204] It is important to take seasonal variations in the 24-hour BP profile into account when assessing 24-hour BP control.[205]

Adjustment of antihypertensive therapy based on 24-hour data from ABPM has been shown to provide the same level of BP control

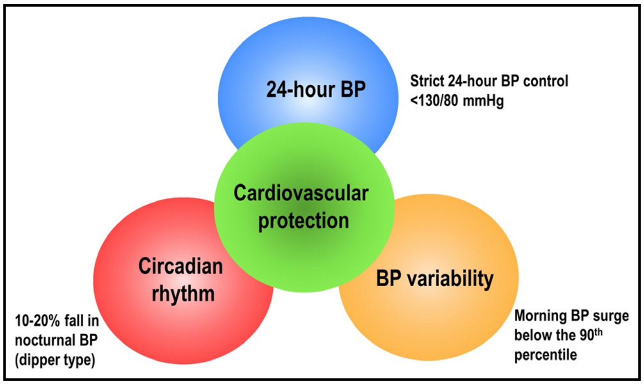

FIGURE 5 Triad of optimal 24-h BP control (reproduced from Kario et al[56])

with less intensive therapy compared with treatment managed using office BP.[206] In addition, the proportion of primary care patients achieving target BP was higher when antihypertensive therapy was managed using ABPM compared with office BP (38% vs 12% in one study and 54% vs 37% in another).[207,208] However, none of the current guidelines make specific recommendations about how to use ABPM to monitor the effectiveness of antihypertensive interventions. The frequency of repeat assessment could be guided by the risk profile of the patient. Repeating ABPM every few months, complemented by home and office BP readings, might be sufficient for low-risk patients. In contrast, tight BP control throughout the 24-hour period is most important in high-risk patients (eg, those with target organ damage, a history of cardiovascular disease, or comorbidities such as diabetes mellitus or CKD) and therefore repeating ABPM every few weeks would provide useful data on whether adequate reductions in BP have been achieved.[209] However, the feasibility and patient acceptability of using ABPM every few weeks in treated patients remain to be determined. Given that patients with moderate to severe renal dysfunction almost always have elevated nighttime BP, regular use of ABPM is beneficial to assess and treat nocturnal hypertension.[210,211]

Longer acting antihypertensive agents provide better control of nocturnal and morning BP. These agents are usually administered once daily in the morning and reduce BP throughout the 24-hour dosing period to attenuate the exaggerated morning BP surge. Diuretics specifically reduce nocturnal BP and normalize circadian patterns of BP, transforming non-dippers into dippers.[212] For the management of BPV, which is common in Asians with hypertension, CCBs are an effective option because their BP-lowering activity is independent of salt sensitivity and salt intake.[108] In addition, reductions in BP during treatment with CCBs are dependent on baseline BP, meaning that the exaggerated morning surge can be effectively reduced without excessive reductions in nighttime BP or that the non-dipper/riser pattern of nocturnal hypertension can be effectively reduced, thus restoring normal circadian rhythm. The CCB amlodipine has been shown to effectively reduce ambulatory BPV.[213] In a meta-analysis of Asian studies (two crossover and nine parallel controlled studies), where ten studies used amlodipine and one used nifedipine gastrointestinal therapeutic system (GITS), the ambulatory BP-lowering effect of CCBs was stronger than that of renin-angiotensin system (RAS) inhibitors, and the slope of the regression lines was comparable for both nocturnal and daytime BP measurements.[108]

Long-acting angiotensin converting enzyme (ACE) inhibitors have been reported to lower ambulatory BP without disruption of diurnal BP variation. As well as reducing BP, suppression of tissue RAS with these agents could contribute to protection against target organ damage and cardiovascular events in patients with hypertension. Nighttime administration of the lipophilic, long-acting ACE inhibitor trandolapril has been shown to significantly decrease pre-awakening and morning SBP, without any excessive fall in nocturnal BP.[214] Treatment with the angiotensin receptor blocker (ARB) candesartan effectively reduced 24-hour and early morning BP on ABPM in patients with essential hypertension, and was more effective than lisinopril for decreasing morning BP and the morning surge in SBP.[215] Alpha-adrenergic and alpha/beta-adrenergic blockers are also effective for reducing the morning BP surge in hypertensive patients. In particular, nocturnal dosing of alpha-adrenergic blockers achieves peak effect in the mornings, providing greater BP reductions during these hours. In the Hypertension and Lipid Trial (HALT), bedtime administration of the alpha-1 blocker doxazosin predominantly reduced morning BP.[216,217] In another study, morning BP and morning BP surge were reduced by bedtime dosing of doxazosin.[177]

Sacubitril/valsartan (LCZ696) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that inhibits neprilysin and the angiotensin (AT_1) receptor, and has potential synergistic activity for cardiovascular protection.[218] ABPM studies showed that sacubitril/valsartan effectively reduced 24-hour BP, including nocturnal BP, in both Western and Asian patients with hypertension.[219,220] Data show that Asian patients with hypertension may respond particularly well to this agent.[221-225]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors significantly reduce 24-hour ambulatory BP, with beneficial effects on both daytime and nighttime BP.[226,227] This has been suggested to be a hemodynamic mechanism underlying the beneficial effects of SGLT2 inhibitors on heart failure in patients with diabetes.[228] The ability of SGLT2 inhibitors to reduce 24-hour BP in salt-sensitive patients[227] suggests that these agents may be suited to the management of Asian patients with hypertension.

Combination antihypertensive therapy is required to achieve good control of BP in many patients. There are a wide variety of combination regimens and fixed drug combinations available, but the most popular are RAS inhibitor-based combinations. Clinical trial data using ABPM suggest that combinations including an ACE inhibitor or ARB plus a CCB effectively reduce 24-hour BP and other ABPM parameters (eg, nocturnal hypertension, morning BP surge) in Japanese patients with hypertension.[229-232] These studies also showed that bedtime antihypertensive dosing has similar effectiveness to morning dosing with respect to control of morning and nighttime BP. If BP is not controlled by dual combination therapy, the triple therapy combination of a RAS inhibitor, a CCB, and a diuretic is the best option in both Asians and Westerners.

Catheter-based renal sympathetic denervation is a new device-based strategy that has recently been introduced for the management of patients with treatment-resistant hypertension. The efferent denervation achieved by this approach reduces renal catecholamine and beta-1 adrenergic renin production. These changes increase renal blood flow and reduce circulating volume, which would contribute to a shift from non-dipping to dipping of nocturnal BP in patients with resistant hypertension. In addition, decreased central sympathetic activity in response to increased baroreceptor sensitivity occurring as a result of afferent denervation could decrease peripheral resistance and the cardiac workload, reducing BPV. It was hypothesized that renal denervation could facilitate excellent 24-hour BP control, with robust reductions in BP, restoration of a dipper pattern of nocturnal hypertension, and reduction in the morning BP surge.[233] Although early results with renal denervation were promising, showing marked and sustained reductions in BP,[234,235] the results of the first randomized trial to include a sham operation arm showed no significant difference between the renal denervation and sham operation groups with respect to the reduction in 24-hour SBP.[236] Nevertheless, analysis of data from that study and a randomized trial conducted in Japan showed that morning BP, nighttime BP, the 2-hour average morning BP, and maximum and moving peak BP were reduced to a greater extent in the renal denervation group vs controls (sham operation or observation only).[237] Certainly, ABPM has been included as an important assessment tool in trials evaluating renal denervation for the treatment of resistant hypertension.[238-240] Further research is required to determine whether renal denervation can effectively and consistently control 24-hour BP. It is currently not recommended as a routine procedure in the latest European or US guidelines.[22,23]

3.12 | Positioning of ABPM in hypertension guidelines

There is a consistent message that ABPM should be used as a diagnostic tool to evaluate hypertension. Guidelines from North America,[37,47] Europe,[16,17] Japan,[21] and China[48] recommend ABPM as the best technology for measuring BP to facilitate the diagnosis of hypertension, and its use in individuals with elevated BP (≥140/90 mm Hg) detected by any means. A summary of recommendations for the use of ABPM in major guidelines is provided in Table 8. No current guidelines provide specific recommendations about the use of ABPM to facilitate the initiation and monitoring of antihypertensive therapy, although emphasis on out-of-office BP measurement (ABPM and HBPM) in clinical practice has increased in the latest revisions of major guidelines.[22,23]

The most comprehensive guidance on the use of ABPM is provided by the ESH position paper,[17] although the main focus is diagnostic use rather than as a method for monitoring the initiation and effectiveness of antihypertensive therapy. This paper does note that the frequency of repeat ABPM for evaluation of antihypertensive medication effectiveness should depend on the severity of hypertension and the response to treatment, being more frequent when hypertension is more severe and in the presence of target organ damage and comorbidities, and less frequent in mild, uncomplicated hypertension—patient preference and physician discretion are suggested as important.[17] For higher risk patients, it has been suggested that repeat ABPM within 2-3 weeks of treatment initiation would provide useful information on whether adequate reductions in BP have been achieved. Then, if adjustments to therapy are required, ABPM could be repeated every 2-3 weeks until stable BP control is documented.[241] After control of both daytime and nighttime ambulatory BP has been achieved, ABPM may only be required every 6-12 months to confirm maintenance of target BP. Although HBPM has a role in the ongoing monitoring of hypertension and its treatment, it is important to note that ABPM is currently the only out-of-office monitoring tool that provides nocturnal BP measurements, which are an important component of BP control.

3.13 | New ABPM indicators and telemedicine

ABPM has traditionally been considered the gold standard for determination of out-of-office BP. However, recent technology developments suggest that use of information and communication technology (ICT)-based devices, which perform automatic, fixed-interval BP measurement during sleep and store or transmit the data (telemedicine), could facilitate a novel approach to patient management.[90] In addition, there are a number of other ICT-based devices that provide important data for optimization of patient management. These include the addition of a nighttime trigger function (where hypoxia and heart rate are determined using pulse oximetry), beat-to-beat continuous surge BP monitoring via a wearable device, and determination of environmental factors (eg, temperature, stress, and exercise). An example of an integrated system collecting both biologic and environmental data is shown in Figure 6, with typical data highlighted in Figure 7. Health information technology (HIT) solutions like this are increasingly being recognized as important advances in health care, and the important and emerging role of HIT was highlighted in the latest version of the ACC/AHA hypertension guidelines.[22] The aim would be to anticipate the occurrence of cardiovascular events based on data obtained by these novel approaches to out-of-office patient monitoring, with the ultimate goal of eliminating the occurrence of cardiovascular events in patients with hypertension. Such an approach is referred to as "anticipation medicine" for zero cardiovascular events,[242] within which BPV is a key biomarker.[3,243]

3.14 | Current use of ABPM in Asia

Despite the positioning of ABPM in guidelines and its use in Asia-based clinical trials, there are limited data on how this important approach to hypertension diagnosis and monitoring is utilized during routine clinical practice in the region. ABPM devices are widely available (twenty-three different devices with ABPM capability in China, twelve in India/Nepal, eleven in Malaysia, ten in Singapore, nine in Japan and Vietnam, eight in South Korea, seven in Hong Kong and the Philippines, five in Pakistan and Indonesia, four in Thailand, and three in Taiwan; Table S1). However, the use of ABPM in clinical practice is influenced by more than just device availability. Other factors that play a role in the decision to use ABPM include cost/reimbursement, patient engagement, physician knowledge and attitude, training/education of both patient and physician, and available resources (both human and financial). Issues such as cost (to the health care system and/or the patient) and practicalities (including scattered populations) will be more of a barrier in developing countries.

A survey conducted in Singapore showed that although nearly three-quarters of physicians who responded said they would recommend ABPM to their patients, only 27% of patients overall were actually given a recommendation for ABPM.[244] The most commonly cited indications for ABPM were diagnosis of resistant hypertension, confirmation of hypertension, evaluation of antihypertensive efficacy, and determination of BPV. Lack of medical consultation

TABLE 8 Summary of international guideline recommendations on when to use ambulatory blood pressure monitoring

Guideline	Diagnosis	Treatment monitoring
ESC/ESH (2018)[23]	• Confirm HTN diagnosis if logistically/economically feasible • Detect white-coat HTN in pts with Grade 1 HTN on office BP measurements, or marked office BP elevation without target organ damage • Detect masked HTN in pts with high-normal office BP, or with normal office BP and target organ damage or high cardiovascular risk • Evaluate postural and post-prandial hypotension • Evaluate resistant HTN • Evaluate exaggerated BP response to exercise • For pts with considerable variability in office BP • Assessment of nocturnal BP and dipping status • Confirm secondary HTN • Determine BP during pregnancy, particularly in high-risk women • Screening for HTN in pts with diabetes mellitus	• Monitor BP control • Evaluation of BP control, especially in treated higher risk pts • Evaluate postural and post-prandial hypotension • Confirm inadequate control of BP indicating treatment resistance
AHA/ACC (2017)[22]	• Confirm HTN diagnosis • Screen for white-coat HTN in adults with untreated BP > 130 to <160/>80 to <100 mm Hg • Periodic monitoring to detect transition to sustained HTN in pts with white-coat HTN • Screen for masked HTN in individuals with office BP consistently between 120/75 and 129/79 mm Hg	• Titration of BP-lowering medication • Confirm white-coat effect in pts with office BP not at goal and HBPM readings indicative of a significant white-coat effect • Screen for white-coat effect in pts receiving multiple drug therapies and office BP ≤ 10 mm Hg above goal • Confirm masked uncontrolled HTN in treated pts with HBPM readings indicative of masked uncontrolled HTN before intensification of treatment
Taiwan (2015)[13]	• Confirm diagnosis of HTN • Identify white-coat HTN • Identify masked HTN • Regular monitoring to detect transition to sustained HTN in pts with white-coat HTN • Evaluate diurnal BP changes	• Identify white-coat HTN • Detect white-coat effect
JSH (2014)[21]	• Confirm diagnosis of HTN when there is marked discordance between office BP and home BP • In pts with home BP 125-134/80-84 mm Hg • In pts with high variability in home BP • Confirm white-coat HTN • Confirm masked HTN • Evaluate dipping status • Evaluate short-term BPV	• Evaluate the effects of treatment and duration of treatment effect • Identify poorly controlled and treatment-resistant HTN
Korea (2013)[248,249]	• Identify white-coat HTN • Identify masked HTN • Identify resistant HTN • Identify labile HTN • Provide accurate BP measurements for risk assessment • Assessment of nocturnal BP and dipping status	• To assist in the diagnosis of resistant HTN
NICE (2011)[16]	• Confirm diagnosis of HTN when clinic BP is ≥140/90 or HTN is suspected	• As an adjunct to clinic BP measurements to monitor the response to antihypertensive treatment

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; BPV, blood pressure variability; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HBPM, home blood pressure monitoring; HTN, hypertension; JSH, Japanese Society of Hypertension; NICE, National Institute for Health and Care Excellence; pts, patients.

time, no access to a suitable device, patient inertia, poor patient compliance, and lack of suitable education materials were cited as challenges to the implementation of out-of-office BP measurement (including ABPM).[244]

In Japan, ABPM is reimbursed by the National Health Insurance scheme, based on the superiority of ABPM over casual measurement of BP for predicting the development of cardio- and cerebrovascular events and the cost effectiveness of this approach.[245] Using a Markov model, it was estimated that introduction of ABPM for hypertension monitoring in Japan would save 10 trillion yen over 10 years, reduce the number of strokes by more than 59 500, and save almost 19 000 lives.[246]

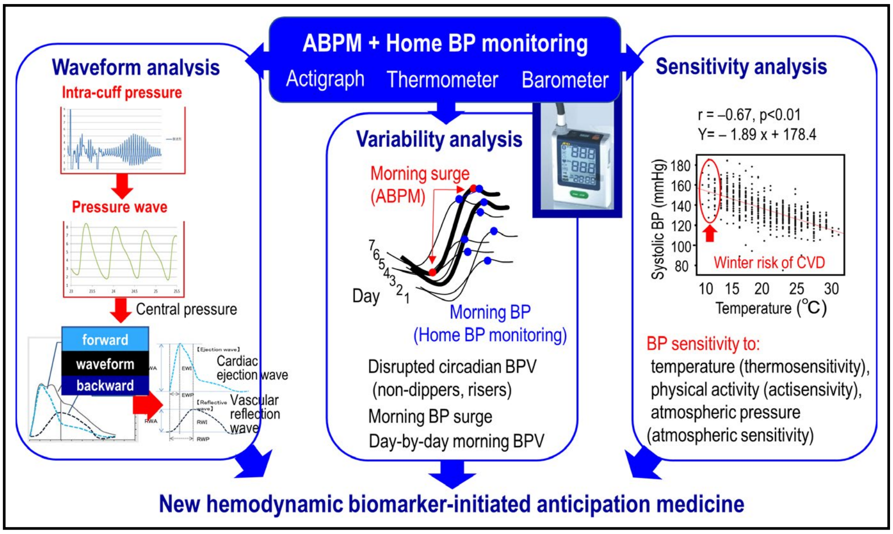

FIGURE 6 New information communication technology-based multisensor approach to ambulatory blood pressure monitoring. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability; CVD, cardiovascular disease; HBPM, home blood pressure monitoring; SBP, systolic blood pressure (reproduced from Kario et al[242] with permission)

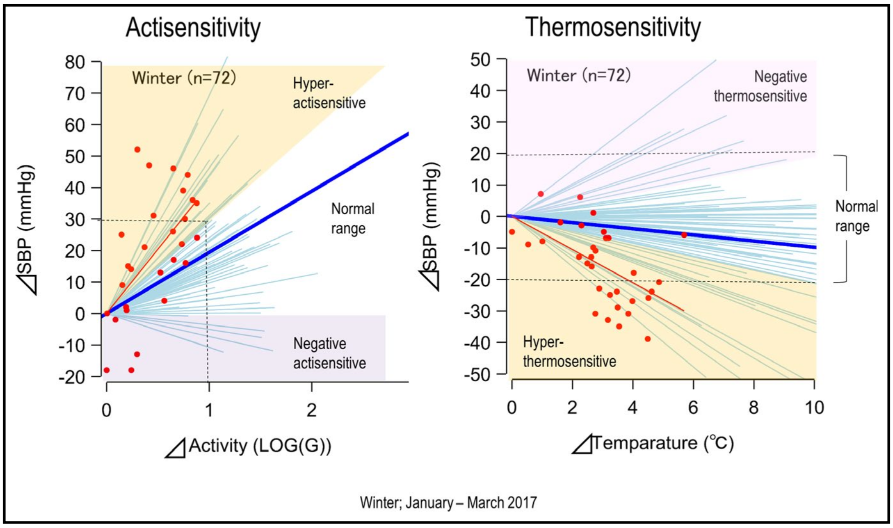

FIGURE 7 Classification of high-risk groups stratified by actisensitivity and thermosensitivity. SBP, systolic blood pressure. Actisensitivity is defined as the slope of SBP change vs physical activity (eg, actisensitive hypertension [hyperactisensitivity] could be defined as a ≥30 mm Hg increase in SBP when physical activity increases from 100G [resting] to 1000G [walking]). Thermosensitivity is defined as the slope of SBP change vs change in temperature (eg, cold thermosensitive hypertension [hyperthermosenstivity] could be defined as a ≥20 mm Hg increase in SBP when temperature decreases by 10°C) (reproduced from Kario et al[243] with permission)

Region-wide strategies are needed to improve access to APBM devices, provide physician training, and develop suitable education materials to facilitate more widespread use of ABPM in Asia.

4 | CONCLUSIONS

ABPM is recognized as an essential part of good clinical practice when diagnosing hypertension. It provides information on BP throughout the 24-hour window, facilitating the diagnosis of white-coat and masked hypertension, and the identification of specific BP and BPV phenotypes. ABPM can also play a role in the effective initiation and management of antihypertensive therapy and allows determination of BP control throughout the 24-hour period. Furthermore, additional clinical trials are needed to determine the benefits of ABPM-guided hypertension management strategies on hard clinical endpoints, which can then inform future guidelines in this important field. Hypertension in Asia is characterized by a number of specific features, many of which (eg, BPV and nocturnal hypertension) are best identified using ABPM. Therefore, ABPM may be particularly useful in Asian populations, improving patient management and the efficient allocation of treatment and health care resources.

CONFLICT OF INTEREST

K Kario received research grants from Omron Healthcare, Fukuda Denshi, A&D, Pfizer Japan, and honoraria from Omron Healthcare. S Park has received research grants and honoraria from Pfizer. S Siddique has received honoraria from Bayer, Novartis, Pfizer, ICI, and Servier; and travel, accommodation and conference registration support from Atco Pharmaceutical, Highnoon Laboratories, Horizon Pharma, ICI, Pfizer and CCL. YC Chia has received honoraria and sponsorship to attend conferences and CME seminars from Abbott, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Menarini, Merck Sharp & Dohme, Novartis, Orient Europharma, Pfizer, and Sanofi; and a research grant from Pfizer. J Shin has received honoraria and sponsorship to attend seminars from Daiichi Sankyo, Takeda, Menarini, MSD, Bristol-Myers Squibb, and Sanofi. CH Chen

has served as an advisor or consultant for Novartis Pharmaceuticals Corporation; has served as a speaker or a member of a speakers bureau for AstraZeneca; Pfizer Inc; Bayer AG; Bristol-Myers Squibb Company; Boehringer Ingelheim Pharmaceuticals, Inc; Daiichi Sankyo, Inc; Novartis Pharmaceuticals Corporation; SERVIER; Merck & Co., Inc; Sanofi; TAKEDA Pharmaceuticals International; and has received grants for clinical research from Microlife Co., Ltd. R Divinagracia has received honoraria as a member of speaker's bureaus for Bayer, Novartis, and Pfizer. J Sison has received honoraria from Pfizer, AstraZeneca, Boehringer Ingelheim and Novartis. GP Sogunuru has received a research grant related to hypertension monitoring and treatment from Pfizer. JC Tay has received advisory board and consultant honoraria from Pfizer. BW TEO has received honoraria for lectures and consulting fees from Astellas, AstraZeneca, Boehringer Ingelheim, Servier, MSD, and Novartis. JG Wang has received research grants from Bayer, Merck Sharp & Dohme, Pfizer, and Phillips; and lecture and consulting fees from Bayer, Daiichi-Sankyo, Merck Sharp & Dohme, Pfizer, Servier, and Takeda. Y Zhang has received research grants from Bayer, Novartis, and Shuanghe; and lecture fees from Bayer, Daiichi Sankyo, Novartis, Pfizer, Sanofi, Servier, and Takeda. All other authors report no potential conflicts of interest in relation to this article.

AUTHOR CONTRIBUTION

(1) Kazuomi Kario MD, PhD and Ji-Guang Wang MD, PhD involved in conception and design of the study. (2) Kazuomi Kario MD, PhD, Jinho Shin MD, Chen-Huan Chen MD, Peera Buranakitjaroen MD, MSc, DPhil, Yook-Chin Chia MBBS, FRCP, Romeo Divinagracia MD, MHSA, Jennifer Nailes MD, MSPH, Satoshi Hoshide MD, PhD, Saulat Siddique MBBS, MRCP (UK), FRCP (Lon), Jorge Sison MD, Arieska Ann Soenarta MD, Guru Prasad Sogunuru MD, DM, Jam Chin Tay MBBS, FAMS, Boon Wee Teo MB BCh (Ireland), Yuda Turana MD, PhD, Yuqing Zhang MD, Sungha Park MD, PhD, Huynh Van Minh MD, PhD, and Ji-Guang Wang MD, PhD drafted the manuscript or critically revised the important intellectual content. (3) Kazuomi Kario MD, PhD, Jinho Shin MD, Chen-Huan Chen MD, Peera Buranakitjaroen MD, MSc, DPhil, Yook-Chin Chia MBBS, FRCP, Romeo Divinagracia MD, MHSA, Jennifer Nailes MD, MSPH, Satoshi Hoshide MD, PhD, Saulat Siddique MBBS, MRCP (UK), FRCP (Lon), Jorge Sison MD, Arieska Ann Soenarta MD, Guru Prasad Sogunuru MD, DM, Jam Chin Tay MBBS, FAMS, Boon Wee Teo MB BCh (Ireland), Yuda Turana MD, PhD, Yuqing Zhang MD, Sungha Park MD, PhD, Huynh Van Minh MD, PhD, and Ji-Guang Wang MD, PhD involved in final approval of the submitted manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX

CONSENSUS TABLES

TABLE A1 Advantages and limitations of ABPM vs office and HBPM readings in clinical practice

Recommendation	Class of recommendation	Level of evidence
1. ABPM is the gold standard to assess 24-h BP, sleep BP, and diurnal BPV	I	A
2. Cuff inflation-related problems can occur during clinical use of ABPM	IIa	C
3. ABPM and HBPM could be used as complementary, rather than alternative, tools	I	B
4. ABPM is useful for detecting ambulatory cardiovascular risk (isolated daytime hypertension, isolated nocturnal hypertension) that cannot be detected using clinic BP and HBPM	IIa	B
5. ABPM is useful for evaluating the 24-h BP-lowering effect of antihypertensive treatments, and for detecting masked uncontrolled hypertension, even when clinic and home BP are well controlled	I	A
6. ABPM would be useful for detecting ambulatory hypotensive episodes (antihypertensive medication-related, postprandial, due to autonomic dysfunction, etc) in patients with hypotensive symptoms (fainting, weakness, sleepiness)	I	A

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability.

TABLE A2 Measurement schedule and assessment of ABPM parameters

Recommendation	Class of recommendation	Level of evidence
1. Ambulatory BP measurement should be performed every 15-30 min during the daytime (awake) period and every 30-60 min during nighttime (sleep) period	I	A
2. Quality of ABPM is considered good when the 24-h recording includes ≥70% of expected measurements, or ≥20 valid daytime and ≥7 valid nighttime measurements are recorded	I	A
3. Diary-based assessment is superior to 24-h clock-based assessment for evaluation of the 24-h BP profile in an individual patient	I	A
4. 24-h BP is defined as the averaged BP values for 24 h; daytime BP is the averaged daytime (awake) BP values, nighttime BP is the averaged nighttime (sleep) BP values, and morning BP is the averaged morning BP values taken in the 2 h after rising	I	A

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

TABLE A3 ABPM-based definitions of hypertension and target BP values

Recommendation	Class of recommendation	Level of evidence
1. ABPM diagnosis of hypertension is based on one of the following: • ≥130/80 mm Hg for average 24-h BP (sustained hypertension) • ≥135/85 mm Hg for average daytime BP (daytime hypertension) • ≥120/70 mm Hg for average nighttime BP (nocturnal hypertension) • ≥135/85 mm Hg for average morning BP (morning hypertension)	I	A
2. Strict ABPM thresholds for hypertension: • ≥125/75 mm Hg for average 24-h BP (hypertension) • ≥130/80 mm Hg for average daytime BP (daytime hypertension) • ≥110/65 mm Hg for average nighttime BP (nocturnal hypertension) • ≥130/80 mm Hg for average morning BP (morning hypertension)	IIa	C
3. White-coat hypertension is defined as • Clinic BP ≥ 140/90 mm Hg AND • ABPM values: 24-h BP < 130/80 mm Hg, daytime BP < 135/85 mm Hg, nighttime BP < 120/70 mm Hg, and morning BP < 135/85 mm Hg	I	A
4. Masked hypertension is defined as • Clinic BP < 140/90 mm Hg AND • ABPM values: 24-h BP ≥ 130/80 mm Hg, daytime BP ≥ 135/85 mm Hg (masked daytime hypertension), nighttime BP ≥ 120/70 mm Hg (masked nocturnal hypertension), and/or morning BP ≥ 135/85 mm Hg (masked morning hypertension)	I	A
5. Masked uncontrolled hypertension is defined as masked hypertension (as per the above definitions) in patients receiving antihypertensive therapy	I	A
6. Conventional goal BP thresholds are: • <130/80 mm Hg for average 24-h BP • <135/85 mm Hg for average daytime BP • <120/70 mm Hg for average nighttime BP • <135/85 mm Hg for average morning BP	IIa	C
7. Strict goal BP thresholds are: • <125/75 mm Hg for average 24-h BP • <130/80 mm Hg for average daytime BP • <110/65 mm Hg for average nighttime BP • <130/80 mm Hg for average morning BP	IIa	C
8. The ideal 24-h BP profile includes the following three components: 24-h BP, adequate diurnal rhythm (dipper-type), and adequate BPV	IIa	B

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability.

TABLE A4 Clinical indications for ABPM

Recommendation	Class of recommendation	Level of evidence
1. ABPM is preferred to precisely diagnose white-coat hypertension and masked hypertension in patients with high-normal home BP (125-134/75-84 mm Hg)	IIa	B
2. For hypertensive patients with normal average home BP (home BP-defined white-coat hypotension or normotension), ABPM is recommended to reliably exclude masked hypertension, especially in patients with comorbidities	IIa	C
3. Evaluation of resistant hypertension in patients with persistently elevated office BP(≥130/80 mm Hg)despite treatment with ≥3 antihypertensive drugs	IIa	B

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

TABLE A5 Assessment and definition of disrupted diurnal BP rhythm

Recommendation	Class of recommendation	Level of evidence
1. Non-dipper pattern is defined as a nighttime SBP/daytime SBP ratio of >0.9, and dipper pattern is defined when this ratio is <0.9	I	A
2. More precisely, riser pattern is defined as a nighttime SBP/daytime SBP ratio >1.0, non-dipper pattern as nighttime SBP/daytime SBP ratio >0.9 and <1.0, dipper pattern as nighttime SBP/daytime SBP ratio >0.8 and <0.9, and extreme dipper pattern as nighttime SBP/daytime SBP ratio <0.8	I	A

Abbreviation: SBP, systolic blood pressure.

TABLE A6 Assessment and definition of morning BP surge and BPV

Recommendation	Class of recommendation	Level of evidence
1. Morning BP surge is calculated as the morning SBP (average of morning SBP values in the 2 h after arising) minus the 1-h average of the lowest nighttime SBP for the sleep-trough surge, and as morning SBP minus the 2-h pre-awakening nighttime BP values for pre-awakening BP surge	I	A
2. Pathological sleep-trough morning SBP surge ranges from ≈35 mm Hg for community-based samples to ≈55 mm Hg for hypertensive patients	IIa	B
3. Short-term BPV parameters include standard deviation (SD), coefficient of variation (CV), average real variability (ARV), variability independent of the mean (VIM) for daytime BP, nighttime BP, weighted SD of 24-h BP values, and peak and trough values for daytime and nighttime BP	IIa	B

Abbreviations: BP, blood pressure; BPV, blood pressure variability; SBP, systolic blood pressure.

TABLE A7 24-h BP characteristics of specific diseases

Recommendation	Class of recommendation	Level of evidence
1. Obstructive sleep apnea is characterized by non-dipper pattern and nocturnal hypertension with increased BPV, which may trigger sleep-onset cardiovascular events	I	B
2. Diabetes mellitus is characterized by non-dipper pattern and nocturnal hypertension, and exaggerates the cardiovascular risk associated with nocturnal hypertension, especially when accompanied by orthostatic hypotension	I	B
3. CKD is characterized by shortened dipping time, non-dipper pattern and nocturnal hypertension, proportional to CKD stage	I	A
4. Renovascular hypertension and endocrine disorders (primary aldosteronism, Cushing syndrome, pheochromocytoma, etc) are likely to have non-dipper pattern and nocturnal hypertension	I	B
5. Specific drugs (NSAIDs, Kanzo [licorice], etc) are likely to induce a non-dipper pattern and nocturnal hypertension	IIa	B

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability; CKD, chronic kidney disease, NSAIDs, nonsteroidal anti-inflammatories.

TABLE A8 Asian characteristics of the 24-h blood pressure profile

Recommendation	Class of recommendation	Level of evidence
1. Optimal 24-h BP control (24-h BP < 130/80 mm Hg, and restoration of normal nocturnal BP and BPV) is particularly important for reducing the risk of cardiovascular events in Asia	I	B
2. Asians are likely to have masked hypertension, including isolated nocturnal hypertension, morning hypertension, and exaggerated morning BP surge	I	B

Abbreviations: BP, blood pressure; BPV, blood pressure variability.

TABLE A9 ABPM parameters and prediction of cardiovascular outcomes

Recommendation	Class of recommendation	Level of evidence
1. The risk of cardiovascular disease (stroke, coronary artery disease, and/or heart failure) is more closely associated with elevated 24-h, daytime, nighttime and/or morning BP on ABPM than with clinic BP	I	A
2. Masked hypertension is associated with a higher risk of cardiovascular disease than normotension or white-coat hypertension	I	A
3. Uncomplicated white-coat hypertension does not increase cardiovascular risk, but white-coat hypertension in the presence of risk factors and/or target organ damage may be associated with greater risk of cardiovascular events compared with normotension	I	A
4. Nocturnal hypertension and non-dipper/riser patterns are associated with increased risk of cardiovascular disease, including heart failure, while exaggerated morning surge and extreme dipping are likely to be associated with atherosclerotic cardiovascular disease	I	A
5. Short-term ambulatory BPV is associated with increased cardiovascular risk	IIa	B

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability.

TABLE A10 ABPM parameters associated with target organ damage

Recommendation	Class of recommendation	Level of evidence
1. Vascular and organ damage in the brain (cognitive dysfunction), heart (hypertensive heart disease), and kidneys (CKD) are more closely associated with 24-h, daytime, nighttime, and/or morning BP evaluated by ABPM than with clinic BP	I	A
2. Masked hypertension is associated with a higher risk of vascular and organ damage than normotension or white-coat hypertension	I	A
3. White-coat hypertension in association with other cardiometabolic risk factors may be associated with a higher risk of organ damage than normotension	I	A
4. Nocturnal hypertension and non-dipper/riser patterns are associated with increased risk of vascular and organ damage in the brain, heart, and kidneys	I	A
5. Exaggerated morning surge and extreme-dipping are likely to be associated with vascular and brain organ damage	I	A
6. Short-term BPV variability is associated with vascular organ damage	IIa	B

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability; CKD, chronic kidney disease.

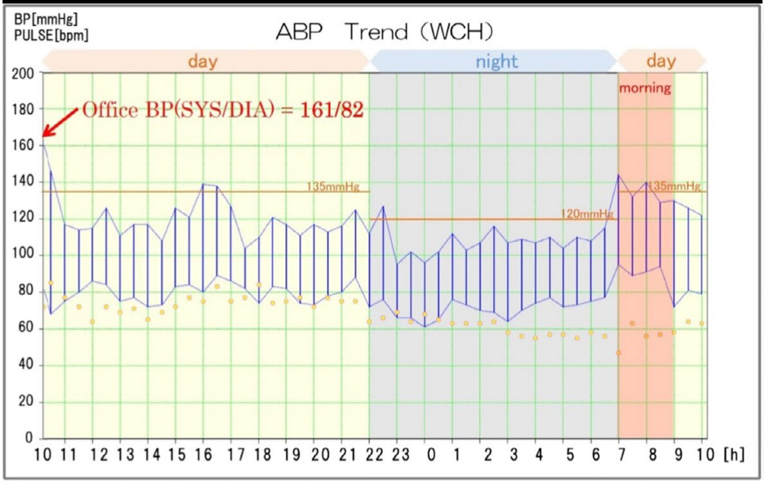
TABLE A11 Antihypertensive treatment assessed using ABPM

Recommendation	Class of recommendation	Level of evidence
1. ABPM can be used to assess the effects of lifestyle modification, antihypertensive medication, and device treatment on the 24-h BP profile	I	A
2. Lifestyle modifications such as diet (salt restriction, fish, vegetables, nuts, etc), regular exercise, good sleeping and housing conditions (temperature, humidity, etc) improve the 24-h BP profile	I	A
3. Seasonal variation in the 24-h BP profile (increased morning BP in winter and increased nighttime BP in summer) should be considered in the assessment of 24-h BP control	IIa	B
4. Long-acting antihypertensive drugs and the combination therapy are useful for reducing 24-h BP	I	A
5. ABPM is useful for detecting uncontrolled morning and nocturnal hypertension during antihypertensive therapy	I	A
6. Antihypertensive interventions that reduce circulating volume (eg salt restriction, diuretics, angiotensin receptor and neprilysin inhibitors and sodium-glucose cotransporter-2 inhibitors) are the preferred approach to reducing nocturnal BP. Long-acting calcium channel blockers effectively reduce daytime BPV and morning BP surge	IIa	B
7. Bedtime antihypertensive drug dosing effectively reduces nocturnal and morning uncontrolled hypertension without excessive daytime hypotensive episodes	I	B
8. Renal denervation is effective at reducing 24-h BP, including nocturnal and morning BP	I	A

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPV, blood pressure variability.

TYPICAL CASES

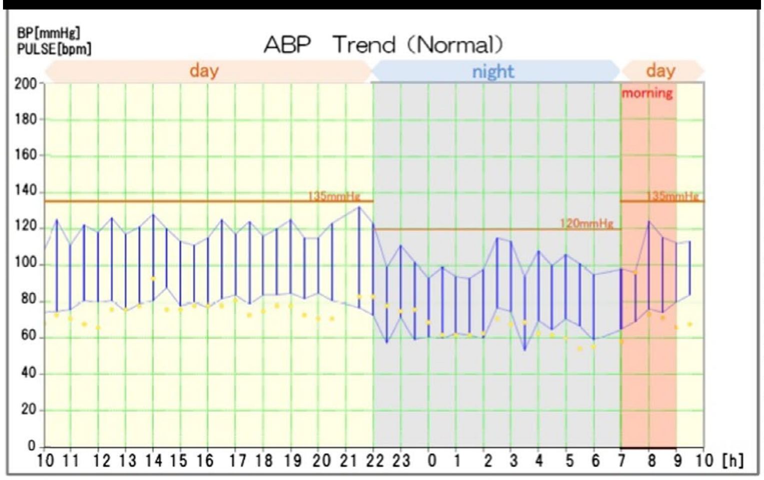
White-coat hypertension pattern



Inspection Item	Value(mmHg)	Standard(mmHg)
Average 24hour (SBP/DBP)	118/77	130/80
Average daytime (SBP/DBP)	124/81	135/85
Average nighttime (SBP/DBP)	109/72	120/70
Average Morning(SBP/DBP)	136/92	135/85
Moving peak morning(SBP)	138	
Maximum morning (SBP)	144	
Average peak nighttime(SBP)	123	
Maximum nighttime(SBP)	127	
Minimum nighttime(SBP)	95	
Moving lowest nighttime(SBP)	99	
Prewakening nighttime(SBP)	108	
S.D. 24hour(SBP/DBP)	13.50/7.81	
C.V. 24hour(SBP/DBP)	11.44/10.11	
Sleep-trough morning surge(SBP)	136-99=37	45 ~55
Dynamic morning surge(SBP)	138-99=39	
Maximum dynamic morning surge(SBP)	144-95=49	
Prewakening morning surge(SBP)	136-108=28	
Average nighttime surge(SBP)	123-109=14	
Dynamic nighttime surge(SBP)	123-99=24	
Maximum dynamic nighttime surge(SBP)	127-95=32	
Nighttime dipping(%)	12%	10%<, ≦20%
Subgroup classification based on nighttime SBP dipping(%)	dipping	

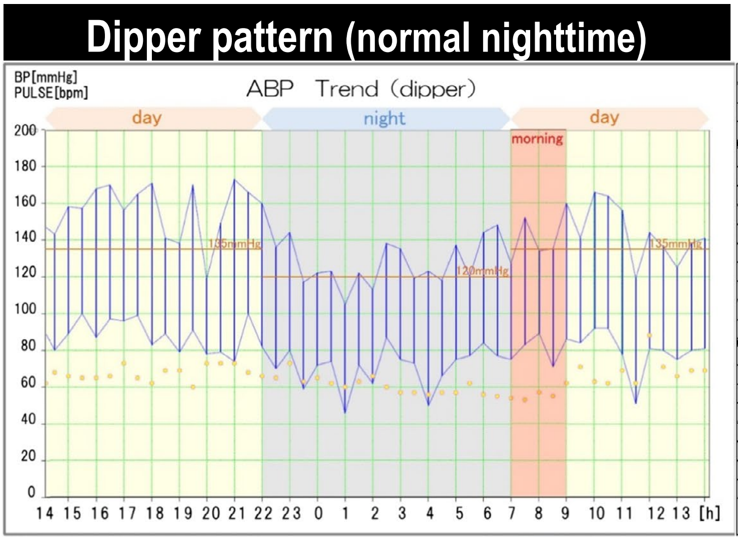
FIGURE A1 Typical ambulatory blood pressure monitoring profile for a patient with white-coat hypertension. ABP, ambulatory blood pressure; BP, blood pressure; bpm, beats/minute; DBP, diastolic blood pressure; SBP, systolic blood pressure (reproduced from Kario, 2018)[56]

Normal pattern



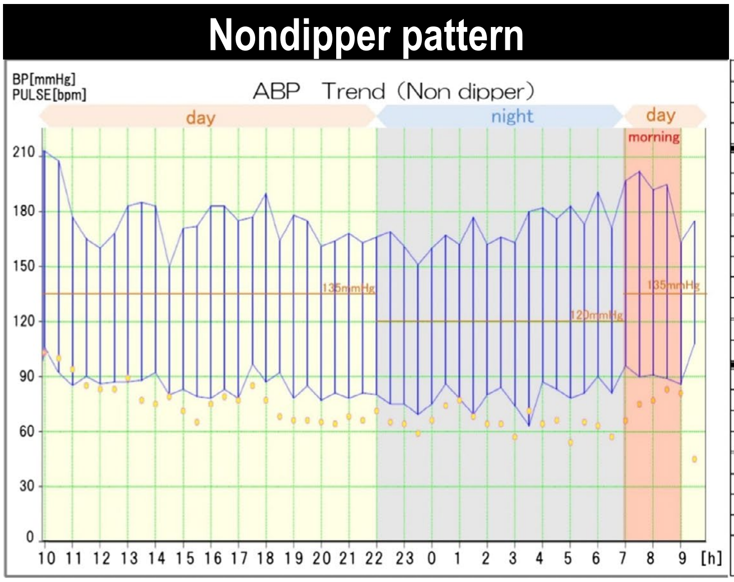
Inspection Item	Value(mmHg)	Standard(mmHg)
Average 24hour (SBP/DBP)	112/74	130/80
Average daytime (SBP/DBP)	118/79	135/85
Average nighttime (SBP/DBP)	101/65	120/70
Average Morning(SBP/DBP)	116/78	135/85
Moving peak morning(SBP)	120	
Maximum morning (SBP)	124	
Average peak nighttime(SBP)	113	
Maximum nighttime(SBP)	115	
Minimum nighttime(SBP)	93	
Moving lowest nighttime(SBP)	93	
Prewakening nighttime(SBP)	96	
S.D. 24hour(SBP/DBP)	10.83/9.01	
C.V. 24hour(SBP/DBP)	9.65/12.14	
Sleep-trough morning surge(SBP)	116-95=21	45 ~55
Dynamic morning surge(SBP)	120-95=25	
Maximum dynamic morning surge(SBP)	124-93=31	
Prewakening morning surge(SBP)	116-96=20	
Average nighttime surge(SBP)	109-101=8	
Dynamic nighttime surge(SBP)	109-95=14	
Maximum dynamic nighttime surge(SBP)	115-93=22	
Nighttime dipping(%)	14%	10%<, ≦20%
Subgroup classification based on nighttime SBP dipping(%)	dipper	

FIGURE A2 Typical ambulatory blood pressure monitoring profile for a patient with normotension. ABP, ambulatory blood pressure; BP, blood pressure; bpm, beats/minute; DBP, diastolic blood pressure; SBP, systolic blood pressure (reproduced from Kario, 2018)[56]



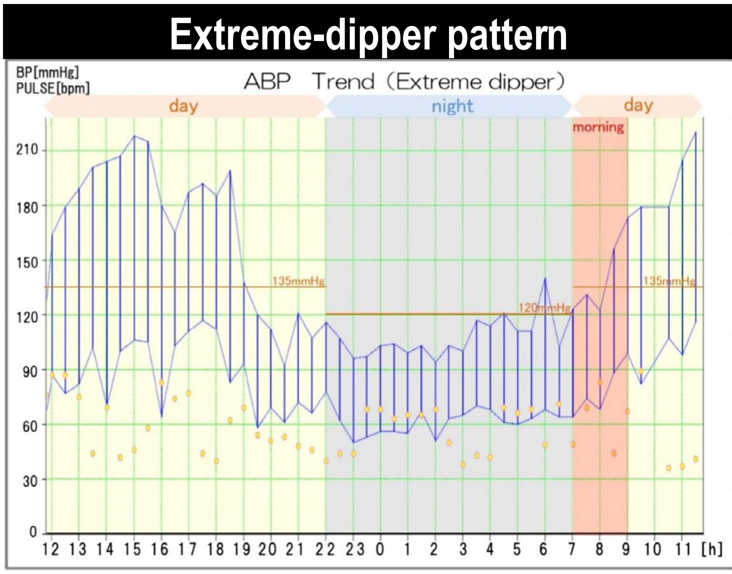
Inspection Item	Value(mmHg)	Standard(mmHg)
Average 24hour (SBP/DBP)	142/79	130/80
Average daytime (SBP/DBP)	149/84	135/85
Average nighttime (SBP/DBP)	127/71	120/70
Average Morning(SBP/DBP)	137/80	135/85
Moving peak morning(SBP)	143	
Maximum morning (SBP)	152	
Average peak nighttime(SBP)	145	
Maximum nighttime(SBP)	148	
Minimum nighttime(SBP)	105	
Moving lowest nighttime(SBP/DBP)	114	
Prewakening nighttime(SBP/DBP)	137	
S.D. 24hour(SBP/DBP)	18.13/12.10	
C.V. 24hour(SBP/DBP)	12.78/15.24	
Sleep-trough morning surge(SBP)	137-114=23	45 ～55
Dynamic morning surge(SBP)	143-114=29	
Maximum dynamic morning surge(SBP)	152-105=47	
Prewakening morning surge(SBP)	137-137=0	
Average nighttime surge(SBP)	145-127=18	
Dynamic nighttime surge(SBP)	145-114=31	
Maximum dynamic nighttime surge(SBP)	148-105=43	
Nighttime dipping(%)	14.8%	10%<、≦20%
Subgroup classification based on nighttime SBP dipping(%)	Dipper	

FIGURE A3 Typical ambulatory blood pressure monitoring profile for a patient with a dipper pattern. ABP, ambulatory blood pressure; BP, blood pressure; bpm, beats/minute; DBP, diastolic blood pressure; SBP, systolic blood pressure (reproduced from Kario, 2018) [56]



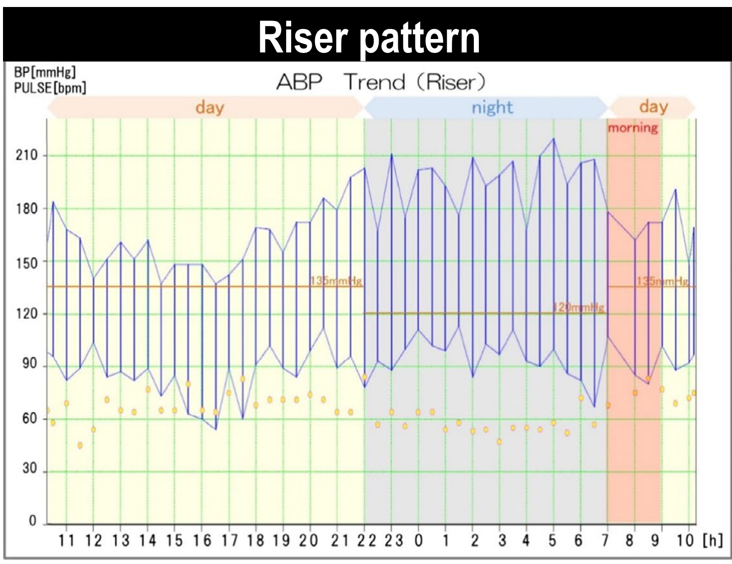
Inspection Item	Value(mmHg)	Standard(mmHg)
Average 24hour (SBP/DBP)	177/84	130/80
Average daytime (SBP/DBP)	180/88	135/85
Average nighttime (SBP)	170/78	120/70
Average Morning(SBP/DBP)	196/95	135/85
Moving peak morning(SBP)	200	
Maximum morning (SBP)	202	
Average peak nighttime(SBP/DBP)	185	
Maximum nighttime(SBP/DBP)	191	
Minimum nighttime(SBP/DBP)	151	
Moving lowest nighttime(SBP/DBP)	156	
Prewakening nighttime(SBP/DBP)	180	
S.D. 24hour(SBP/DBP)	15.64/9.00	
C.V. 24hour(SBP/DBP)	8.86/10.66	
Sleep-trough morning surge(SBP)	196-156=40	45 ～55
Dynamic morning surge(SBP)	200-156=44	
Maximum dynamic morning surge(SBP)	202-151=51	
Prewakening morning surge(SBP)	196-180=16	
Average nighttime surge(SBP)	185-170=15	
Dynamic nighttime surge(SBP)	185-156=29	
Maximum dynamic nighttime surge(SBP)	191-151=40	
Nighttime dipping(%)	5%	10%<、≦20%
Subgroup classification based on nighttime SBP dipping(%)	Non dipper	

FIGURE A4 Typical ambulatory blood pressure monitoring profile for a patient a non-dipper pattern. ABP, ambulatory blood pressure; BP, blood pressure; bpm, beats/minute; DBP, diastolic blood pressure; SBP, systolic blood pressure (reproduced from Kario, 2018) [56]



Inspection Item	Value(mmHg)	Standard(mmHg)
Average 24hour (SBP/DBP)	150/75	130/80
Average daytime (SBP/DBP)	169/81	135/85
Average nighttime (SBP)	105/60	120/70
Average Morning(SBP/DBP)	138/64	135/85
Moving peak morning(SBP)	149	
Maximum morning (SBP)	157	
Average peak nighttime(SBP)	117	
Maximum nighttime(SBP)	121	
Minimum nighttime(SBP)	94	
Moving lowest nighttime(SBP)	97	
Prewakening nighttime(SBP)	114	
S.D. 24hour(SBP/DBP)	40.61/17.72	
C.V. 24hour(SBP/DBP)	27.03/23.65	
Sleep-trough morning surge(SBP)	138-97=41	45 ～55
Dynamic morning surge(SBP)	149-97=52	
Maximum dynamic morning surge(SBP)	157-94=63	
Prewakening morning surge(SBP)	138-114=24	
Average nighttime surge(SBP)	117-105=12	
Dynamic nighttime surge(SBP)	117-97=20	
Maximum dynamic nighttime surge(SBP)	121-94=27	
Nighttime dipping(%)	37.9%	10%<、≦20%
Subgroup classification based on nighttime SBP dipping(%)	Extreme dipper	

FIGURE A5 Typical ambulatory blood pressure monitoring profile for a patient with an extreme-dipper pattern. ABP, ambulatory blood pressure; BP, blood pressure; bpm, beats/minute; DBP, diastolic blood pressure; SBP, systolic blood pressure (reproduced from Kario, 2018)[56]



Inspection Item	Value(mmHg)	Standard(mmHg)
Average 24hour (SBP/DBP)	175/90	130/80
Average daytime (SBP/DBP)	165/87	135/85
Average nighttime (SBP/DBP)	196/97	120/70
Average Morning(SBP/DBP)	197/85	135/85
Moving peak morning(SBP)	207	
Maximum morning (SBP)	208	
Average peak nighttime(SBP)	214	
Maximum nighttime(SBP)	220	
Minimum nighttime(SBP)	167	
Moving lowest nighttime(SBP)	185	
Prewakening nighttime(SBP)	198	
S.D. 24hour(SBP/DBP)	22.88/13.60	
C.V. 24hour(SBP/DBP)	13.06/15.13	
Sleep-trough morning surge(SBP)	197-185=12	45 ～55
Dynamic morning surge(SBP)	207-185=22	
Maximum dynamic morning surge(SBP)	208-167=41	
Prewakening morning surge(SBP)	197-198=-1	
Average nighttime surge(SBP)	214-196=18	
Dynamic nighttime surge(SBP)	214-185=29	
Maximum dynamic nighttime surge(SBP)	220-167=53	
Nighttime dipping(%)	-18%	10%<、≦20%
Subgroup classification based on nighttime SBP dipping(%)	Riser	

FIGURE A6 Typical ambulatory blood pressure monitoring profile for a patient with a riser pattern. ABP, ambulatory blood pressure; BP, blood pressure; bpm, beats/minute; DBP, diastolic blood pressure; SBP, systolic blood pressure (reproduced from Kario, 2018)[56]